Postpartum Haemorrhage and Synthetic Oxytocin Dilutions in Labour

by

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How to administer the 'recommended dosage range' via 'variable speed motor-driven infusion pump'

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How to administer the licensed 'recommended dosage range' via 'variable speed motor-driven infusion pump'.

Abstract

The reason for this study was a growing awareness of excessive rates of postpartum haemorrhage in association with unlicensed synthetic oxytocin use. The pain-inducing property of synthetic oxytocin has standardised introducing epidural analgesia prior to infusion, adding complexity to intrapartum care and greater risks of complex births.

Surmising that research preceded granting synthetic oxytocin its licence, we discovered that when infused slowly, experimental interventions had produced improved outcomes in certain cases. We compared current synthetic oxytocin regimes from across the UK with the licensed instructions.

Unlicensed synthetic oxytocin dilutions and increments, desensitising of oxytocin receptors and unmeasured error factors in infusion pumps, affect labour outcomes and postpartum haemorrhage rates.

The fetus is adversely affected by epidural drugs and by acidosis.

Failure to inform women of intended unlicensed practices with synthetic oxytocin, or obtain Consent for such, or offer licensed practice as standard, constitutes neglect of legal obligations to protect patients, imposed upon doctors and midwives by their professional Codes of Practice.

Our term, 'fine-tuning', describes dosage changes of 0.5 mIU / minute.

The challenges to administering synthetic oxytocin arising from unlicensed dilutions and increments, and variations in pump accuracy, are **all solved by fine-tuning** 0.5 mIU at a time of the licensed dilution - 5 IU in 500 ml - using the lowest effective dosage rate of forty available to support homeostasis, **with the contractions and maternal oxytocin**.

Preface

This paper is about *how* to use synthetic oxytocin when appropriate, taking full advantage of the detailed advice and safety measures described in the licensed instructions to achieve best practice (that is: 'do no harm').

One of the Royal College of Obstetricians and Gynaecologists' suggested dilutions - 30 IU in 500 ml - is not discussed in the article due to word count constraints. We acknowledge it here as it is used in many hospitals.

The mixture contains 60 mIU per ml, which can be written as 1 ml per hour and reinterpreted to 1 mIU per minute to comply with the spirit of the licensed instructions. It looks right, but is impractical, as fine-tuning by 0.5 mIU in 1/120 ml (0.00833 ml) cannot be logged accurately into the infusion pump, as peristaltic (volumetric) pumps and syringe drivers are limited by 2 decimal places after the point. (We do not discuss any other infusion control devices.)

Although some numbers in that scale could be logged, others are impossible, thus potentially depriving the patient of the full range of infusion rates that could be available to optimise contractions safely.

Because volumetric pumps are less accurate at their slowest rates (manufacturers' literature informs us), they can be run faster to infuse low doses of synthetic oxytocin more accurately when the larger licensed volumes of diluent are used. This simplifies the number system to be logged into the pump for dosage changes, which is a great safety feature.

8 mIU - 10 mIU/minute is <60 ml/hour (or 600 ml (1 pint) over 10 hours), a reasonable hydration rate for a woman in labour - unless pre-existing medical conditions attract closer attention to fluid balance. In those cases, the full licensed dosage range should be on offer, despite using less diluent.

This paper is not a discussion about reasons for using synthetic oxytocin.

We are convinced from our research that failure to follow every detail of the licensed instructions is associated with higher postpartum haemorrhage rates.

Introduction

Personal reflection

'Listening to women and their families' experiences in debrief and antenatal clinics between 2014 and 2018, reveals that the impact of massive bleeds is enormous and lasts for years, causing fear not only to themselves but also to family and friends. This fully justifies historical efforts by obstetricians and midwives to prevent maternal morbidity and death from postpartum haemorrhage (Stallworthy, 1939; Brown, 1962, 1968; Chukudebelu et al, 1963; Embrey et al, 1963; Kemp, 1963; Patterson, 1964; O'Driscoll et al, 1969; Arthure et al, 1972; Brinsden and Clark, 1978; Brinsden and Clark, 1979; Weeks et al, 2021).

Although I had observed minute blood losses after spontaneous labours in my early career, having gone back to work on a labour ward again, I was astonished to find major postpartum haemorrhage being normalised by some midwives and obstetricians.

Keenly aware of professional accountability, the Duty of Candour and a responsibility to uphold the Nursing and Midwifery Council's Code (2018), and since women have not changed, I concluded that changes had occurred within obstetric practice (Ford et al, 2007; Knight et al, 2009); which I soon verified by comparing the licensed instructions in the box of synthetic oxytocin ampoules (Mylan, 2019), with the local regime for syringe drivers. They were significantly different. But why had practice been changed?' - *M Tolofari*

Discovery

After an extensive search online, we discovered that synthetic oxytocin, although licensed, is being used in an unlicensed manner in British midwifery on explicit advice from the Royal College of Obstetricians and Gynaecologists (RCOG) 2001, **Figure A**).

Without reference to the role of endogenous oxytocin in induced labour, or to informed patient consent for unlicensed dilutions, increments and new maximum rate, the 2001 dosage advice was re-endorsed by an RCOG-published review commissioned by the National Institute for Health and Care Excellence (National Collaborating Centre for British Women's and Children's Health, 2008).

Hypothesis

If licensed dilutions and dosage options for synthetic oxytocin (one-to-one care and fine-tuning) were employed, postpartum haemorrhage rates would fall below 7% overall, as recorded prior to 1980 (Brinsden and Clark, 1978, 1979), and hasten the reinstatement of procedures expressly for informed consent from women for any unlicensed synthetic oxytocin practices.

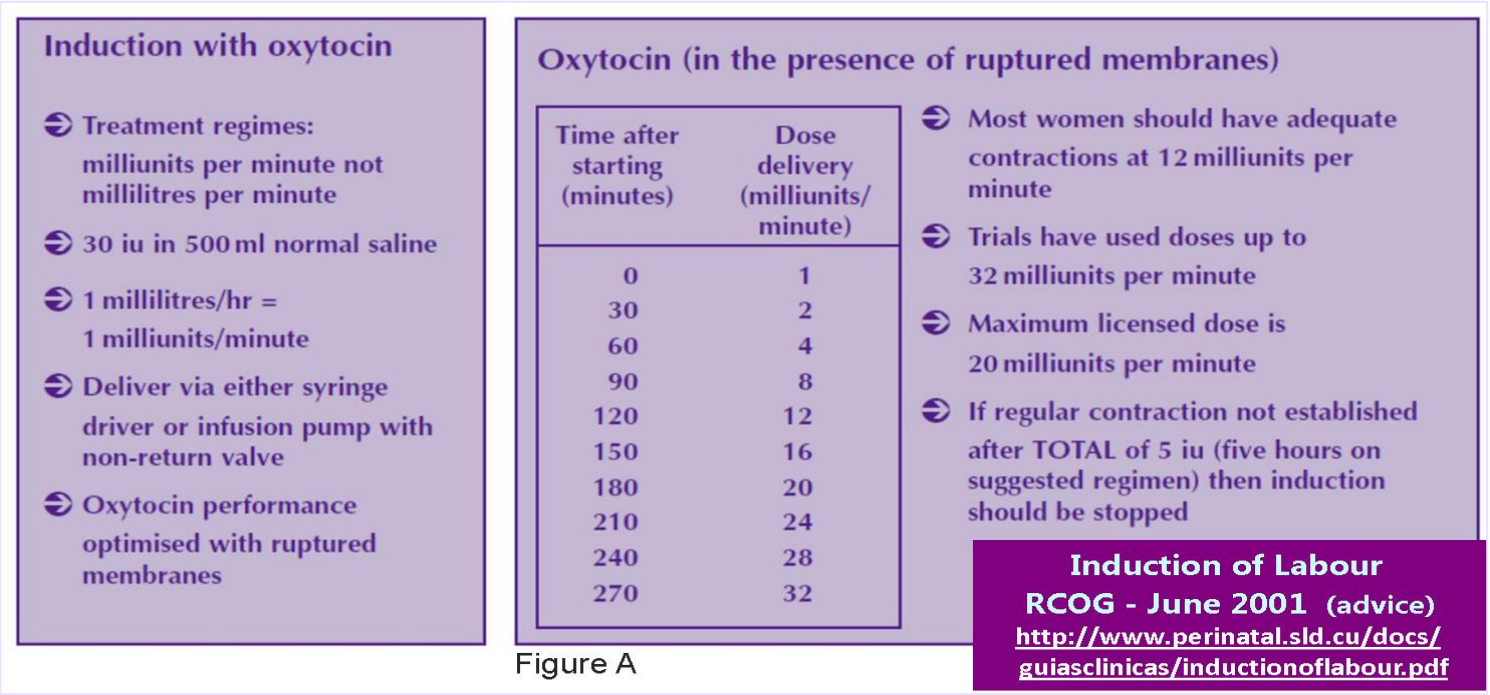

Figure A

Methodology

We reviewed key research before and after synthetic oxytocin (1953) to understand the globally-accepted licensed instructions as they still stand today (developed by manufacturer Novartis, pre 1977 - 2018) noting the British National Formulary departs from them; read discussions between obstetricians about PPH rates in medical journals before 1980; surveyed PPH statistics from NHS Digital (2017, 2018); reviewed online synthetic oxytocin policies and regimes for compliance with the licence; reviewed pump specifications and met with a manufacturer of motorised infusion devices; and we investigated fetal and maternal acidosis.

We sent a freedom-of-information request to all UK maternity units (2019), requesting their infusion devices, synthetic oxytocin regimes and blood loss statistics.

Key findings of Freedom of Information survey

- >90% of induction of labour / synthetic oxytocin regimes were returned
- All appeared to follow RCOG Guidelines except 3
- Policies contained no evidence of Consent for unlicensed practice, or fine-tuning
- Makes and models of volumetric pumps and syringe drivers varied more than expected
- Overall PPH rates are 15% – 50% (NHS Digital, Maternity Statistics, 2017 - 2019)

Other findings

Maternity Dashboard statistics for PPH >1500 ml ranged from 1% - 6%.

Desensitisation of uterine oxytocin receptors occurs in the presence of excess oxytocin (Leng 2016).

Standard pump error factors came to our attention via their published specifications.

From the journal literature search, we noted:

Oxytocin is identical in all species naturally producing it (Lee et al, 2011).

Bovine post-pituitary extract use preceded oxytocin synthesis (Theobald et al, 1948).

PPH rates (20 oz = 550 ml) were typically 3% - 5% (Brinsden and Clark, 1978).

1960s - PPH fatalities (Arthure et al, 1972)

Berde (1965) comments that obstetricians calculate bovine oxytocin / synthetic oxytocin on '1 mg = 450,000 milliunits'. He observed moderate lowering of blood pressure (BP) after experimental pharmacological doses of synthetic oxytocin, acceding to Theobald that physiological dilutions better replicate the hormonal action, including mild hypotension (Pinkerton, 1965).

Via previous administration systems, infusions ran at 40 larger drops per minute and oxytocin concentration could be increased (Barley and Ripman 1970 - illustrated). Normington (1972), researched three standardised dilutions.

Theobald et al (1948) noted that too concentrated a solution of bovine post-pituitary extract induced 'irregularity of the fetal heart', leading to their advocacy of well-diluted solutions at 5 mIU / minute for all cases, including successful, **pre-** eclamptic fit, labour induction (Theobald, Dec 1959).

While respectfully acknowledging Calderyo-Barcia's maximum of 8 mIU / minute, Theobald (1965) asserts -

> *'... it has never been shown that the pharmacological drip is more effective than the physiological one, and it is certainly less safe'.*

No subsequent study of pharmacological doses confirms benefit in every measurable outcome category.

Respecting this 'powerful hormone' (Theobald June & Sept, 1966), we strongly advocate that the full 'recommended dosage range' be re-embedded in local synthetic oxytocin policies, to restore the ***gentle ramp*** of infusion rates missing from the RCOG's **steps** regime **(Figure B)**.

Figure B

5 IU synthetic oxytocin in 500 ml

THE LICENSED DILUTION

Full licensed dosage range: mIU / minute

0.5	1	1.5	2	2.5	3	3.5	4
4.5	5	5.5	6	6.5	7	7.5	8
8.5	9	9.5	10	10.5	11	11.5	12
12.5	13	13.5	14	14.5	15	15.5	16
16.5	17	17.5	18	18.5	19	19.5	20

Maximum licensed rate = 20 mIU / min 24 28 32

The RCOG's regime is highlighted in blue showing all rates omitted by it and unlicensed increments of 4 mIU at a time, up to 32 mIU.

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Appreciating and analysing women's care needs

We use the term patient to draw attention to the status of a (healthy) pregnant woman now receiving synthetic oxytocin infusion, changing from *normal* to ***highly-dependent obstetric care*** due to the risks of synthetic oxytocin infusion (Pinkerton, 1964) and an epidural cannula and anaesthetic drugs (if chosen), during labour.

As unlicensed regimes flowed from experimental research which *intentionally varied* dilutions and increments from the advice licensed, midwives are empowered (NMC, 2018), to inform families of the licensed alternatives, and support women who, choosing one of them, now have a wider choice of pain-relief (Tracy and Tracy, 2003; Walsh, 2009).

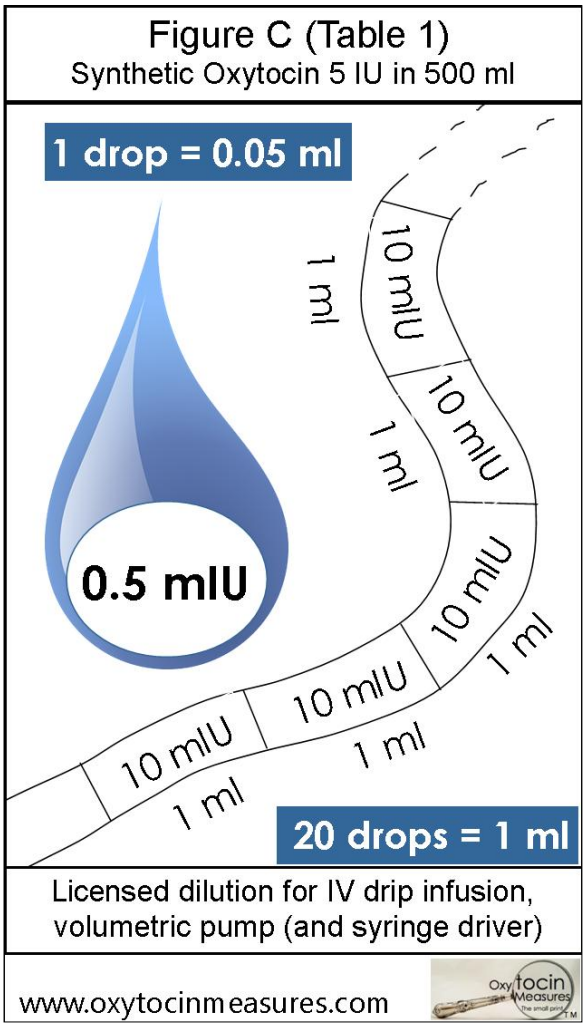
Calibration of synthetic oxytocin for intravenous infusion

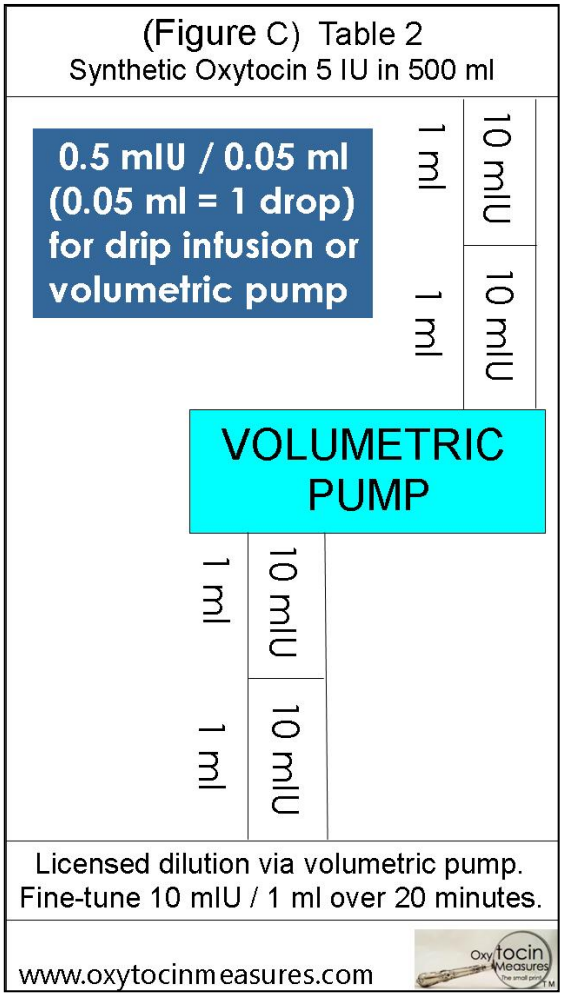
Synthetic oxytocin by weight

- International Units (IU) define organic (bio-) chemicals.
- **1 mg = 600 IU** biological activity (World Health Organization, 2010).

Synthetic oxytocin by weight in diluent

1 ml ampoules of synthetic oxytocin come as 5 IU or 10 IU concentrate, which contain 8.3 - 8.5 micrograms or 16.66 - 17 micrograms respectively (Ever, 2018, Mylan, 2019) , **Figure C, (Key** and **Table 1,** P6), **(Figure C), Table 2**, P7).





Drip infusion calculation

As some practitioners across the world work without electricity, the 'recommended dosage range' is based on the standard dilution for drip infusion: 5 IU in 500 ml.

To find mIU in 1 drop

Tools
1 ml = 20 drops
1 IU = 1,000 mIU

5 IU = 5,000 mIU / 500 (ml) = 10 mIU / ml

10 mIU / 20 (drops) = half (½) 1 mIU / drop

∴ 1 drop contains 0.5 mIU synthetic oxytocin (See SmPC)

If 1 drop = 1 (ml) ÷ 20, then 1 drop = 0.05 ml

∴ 8.3 microgram / 5,000 mIU = 0.00166 microgram / mIU

∴ 0.00166 / 2 = **0.00083 microgram per drop** or **0.5 mIU / 0.05 ml**

KEY to synthetic oxytocin drip infusion and for volumetric pump

In the table below **drops** match **mIU location** and **ml location**.

Numbers in bold have no additional therapeutic meaning.

	milliunits (mIU) / minute				Volume (ml) / minute			
A	**0.5**	1	1.5	2	**0.05**	0.1	0.15	0.2
B	10.5	11	11.5	12	1.05	1.1	1.15	1.2
	18.5	19	19.5	**20**	1.85	1.9	1.95	**2.0**

Rate changes of 0.5 mIU / minute x 20 minutes = 10 mIU (more, or less)
NOTE: volume variations will depend on the dilution being infused.

Table 1 (drop / mIU / ml)
5 IU Synthetic Oxytocin in 500 ml for drip infusion (10 mU / ml)

	0.5 mIU / drop				Total mIU / no of drops				Volume (0.05 ml / drop)			
A	1	2	3	4	0.5	1	1.5	2	0.05	0.1	0.15	0.2
	5	6	7	8	**2.5**	3	3.5	4	**0.25**	0.3	0.35	0.4
	9	**10**	11	12	4.5	**5**	5.5	6	0.45	**0.5**	0.55	0.6
	13	14	**15**	16	6.5	7	**7.5**	8	0.65	0.7	**0.75**	0.8
	17	18	19	**20**	8.5	9	9.5	**10**	0.85	0.9	0.95	**1.0**
B	21	22	23	24	10.5	11	11.5	12	1.05	1.1	1.15	1.2
	25	26	27	28	**12.5**	13	13.5	14	**1.25**	1.3	1.35	1.4
	29	**30**	31	32	14.5	**15**	15.5	16	1.45	**1.5**	1.55	1.6
	33	34	**35**	36	16.5	17	**17.5**	18	1.65	1.7	**1.75**	1.8
	37	38	39	**40**	18.5	19	19.5	**20**	1.85	1.9	1.95	**2.0**

Synthetic Oxytocin in drops / minute, mIU / drops and ml / no of drops
A 1 drop - 20 drops / minute **B** 21 drops - 40 drops / minute

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Table 1 shows how to relate the full range of licensed dosages (for live pregnancy) by drip infusion, to volumes-to-be-infused (VTBI) via infusion pump.

Table 2: *Drip infusion measures multiplied for volumetric pump settings.*

Table 2
(mIU / 1 and 20 minutes / 20 minute VTBI ml)
LICENSED DILUTION - 5 IU Synthetic Oxytocin in 500 ml
for Drip Infusion, Volumetric Pump or Syringe Driver

	mIU / minute				mIU / 20 minutes				ml / 20 minutes			
A	0.5	1	1.5	2	10	20	30	40	1	2	3	4
	2.5	3	3.5	4	**50**	60	70	80	**5**	6	7	8
	4.5	**5**	5.5	6	90	**100**	110	120	9	**10**	11	12
	6.5	7	**7.5**	8	130	140	**150**	160	13	14	**15**	16
	8.5	9	9.5	**10**	170	180	190	**200**	17	18	19	**20**
B	10.5	11	11.5	12	210	220	230	240	21	22	23	24
	12.5	13	13.5	14	**250**	260	270	280	**25**	26	27	28
	14.5	**15**	15.5	16	290	**300**	310	320	29	**30**	31	32
	16.5	17	**17.5**	18	330	340	**350**	360	33	34	**35**	36
	18.5	19	19.5	**20**	370	380	390	**400**	37	38	39	**40**

Volumes containing the recommended dosage range for 1 and 20 minutes.
A Start rates for augmentation. Maximum start for induction = 4 mIU / minute
<10 mIU / minute = average rate; **B** upper range to maximum 20 mIU / minute.

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Pre-prostaglandin era

The instructions agreed by the (then) UK licensing body, balanced more synthetic oxytocin in less diluent for fewer drops per minute (via modern giving set) to address medical concerns about water intoxication, advising that if only irregular (or no) contractions occurred during the first 5 IU infused, the infusion should stop overnight.

The product design (based on pre-synthetic oxytocin research) aims to promote 'a contraction pattern similar to that of normal labour' (Mylan, 2019), offering a straightforward system for measuring and calculating doses based on one accurately-calibrated mixture, weak enough to individualise by fine-tuning in titration with the patient's own oxytocin and contractions, or be halved or doubled as clinically indicated.

Patient stability and fetal wellbeing are safeguarded by the expertise that was given to determining and wording the licensed instructions - as long as the infusion is managed accordingly.

Changes to the licensed instructions, 1977 *(Novartis, 1977)*

1) Delay the infusion for 6 hours after prostaglandins therapy.
2) Use a motor-driven, variable-speed infusion pump if possible.

Dilution

We use the word dilution when synthetic oxytocin concentrate is diluted for clinical use, whether or not the resulting infusible mixture is 'physiological' - licensed for pregnancy - or strong enough to be deemed a drug (pharmacological - unlicensed for pregnancy).

Three licensed dilutions

i) 5 IU in 500 ml diluent is the standard dilution.

Start rates are 0.5 - 4 mIU / minute. Subsequent rate increases must range between 0.5 mIU and 2 mIU / minute **only.**

ii) 10 IU in 500 ml (20 mIU / ml) after intrauterine death.

iii) 20 IU in 500 ml to prevent or manage PPH.

All unlicensed practices oblige clinical justification and valid, informed patient Consent, to be **legal**.

Unlicensed practices

- **Any intramuscular injection >5 IU** - 10 IU, and 20 IU or 30 IU in theatre post-Caesarean (Svanstrom et al, 2008).

- **Synthetic oxytocin concentrate not fully diluted** before intravenous administration.

- **40 IU in 500 ml diluent.** When the licensed dilution has been used in labour (or none), 20 IU in 500 ml will control PPH.

- **To exceed 20 mIU / minute during labour (Figure B,** P4**)**, an experienced obstetrician should examine the patient for clinical indications for this new unlicensed treatment. **The dose must be separately prescribed to proceed**.

These unlicensed uses after labour - without formal patient consent - are illegal.

1. Intramuscular injection >5 IU synthetic oxytocin (instead of Syntometrine 1 ml)

2. 40 IU synthetic oxytocin in 500 ml diluent (instead of 20 IU in 500 ml)

3. Intravenous bolus of any dose synthetic oxytocin for any reason at any speed

De-sensitisation of oxytocin receptors

Theobald (Feb 1959) had unwittingly elicited oxytocin receptor desensitisation before it was formally identified. So, I *(MT)* asked Dr Gareth Leng (2016), Professor of Experimental Physiology at Edinburgh University, a private question:

Can too much synthetic oxytocin block the release of natural oxytocin?

He said: ***'… If you give too much oxytocin [synthetic oxytocin] when the uterus is fully ready – when there are lots of [oxytocin] receptors – you will get a strong initial response but you won't sustain that response, because again the receptors will disappear [inside the cell]. You need to give enough to activate the receptors, but not so much that you desensitise them …'***

(Dawood, 1995, Vrachnis et al, 2011).

We suggest that correct use of the recommended dosage options accommodates this sensitivity, which is obliquely raised by Weeks and Neilson in, *Rethinking our Approach to Postpartum Haemorrhage and Uterotonics* (2015).

Pump error factors

An error factor is the permitted ± percentage variation in accuracy during use, specified by the hardware's manufacturer. Each pump at its best has a unique, inbuilt error factor, which, since synthetic oxytocin causes pain, adds another cause for caution to synthetic oxytocin administration, and reason for fine-tuning with contractions.

Volumetric pumps ± 5% to ±10% at very slow rates, militating against unlicensed concentrations where VTBI times would be lengthened to attempt fine-tuning (to accommodate the widening error factor). Syringe drivers ± 2%.

10 IU in 1 ml synthetic oxytocin added to 49 ml diluent (in syringe drivers) provides 200 mIU / ml that is **20** times stronger than licensed for live pregnancy. **Figure D**, **Table 4** (P13), shows the volumes required to administer the licensed dosage range.

The stronger the synthetic oxytocin concentration, the higher the mIU in the smallest volumes (after the decimal point) for VTBI, affecting ease of fine-tuning.

Consider 5 IU in 50 ml (**Figure G, Table 5,** P15) or 2.5 IU in 50 ml (**Figure H, Table 6,** P16), for syringe drivers, instead.

Managing synthetic oxytocin by motor-driven infusion pump

Disable the bolus function

On the pump, or in its software, the bolus option should be disabled permanently or routinely prior to synthetic oxytocin infusion, because with unlicensed dilutions even a fail-safe-sized bolus may elicit an adverse maternal or fetal response. Technical help or a password may be needed. Motorised infusion devices vary, so it is important to comply with each one's specific operational routines and limitations to administer synthetic oxytocin safely. **Figure E (Table of Dilutions)**, lists current unlicensed dilutions and licensed alternatives.

Figure E

Table of Dilutions of Synthetic Oxytocin for Intravenous Infusions

Unlicensed dilutions Licensed dilutions

Method	Diluent (ml)	IU added	Milliunits (mIU)	mIU /ml	Information	Tables and Figures
Volumetric	500	5	5,000	10	Licensed dilution	Table 2 - **Figure C**
Volumetric	500	2.5	2,500	5	Half-strength	Table 3 - **Figure F**
Drip Infusion	500	2.5	2,500	5	Half-strength	Table 3 - **Figure F**
Drip Infusion	500	5	5,000	10	Licensed dilution	Table 1 - **Figure C**
Drip Infusion	1,000	10	10,000	10	Licensed dilution	Table 1 - **Figure C**
IMPORTANT NOTE - 20 mU / ml (next below) is **licensed ONLY for after intrauterine death**. The RCOG's advice for live pregnancies includes this and allows for other irregular dilutions.						**Figure A** **Figure B**
Drip Infusion	1,000	10 x 2	20,000	20	RCOG regime	Note: volumes as Table 1 and 2 + mIU doubled.
Drip Infusion	500	10	10,000	20	RCOG regime	
Volumetric	500	10	10,000	20	RCOG regime	
Volumetric	500	10 x 3	30,000	60	RCOG regime	Low rate = ↑ error factor
Syringe Driver **(Table 4)** for 10 IU in 50 ml shows VTBI volumes / 30 minutes cannot be logged accurately. Do not round up incomplete numbers. Rather, drop the 3rd decimal digit, or use 20 minute VTBI settings.						
Syringe Driver	49	10	10,000	200	0.5 mIU/0.0025 ml	Table 4 - **Figure D**
Syringe Driver	49	5	5,000	100	0.5 mIU/0.005 ml	Table 5 - **Figure G**
Syringe Driver	49.5	2.5	2,500	50	0.5 mIU/0.01 ml	Table 6 - **Figure H**
5 IU in 50 ml and 2.5 IU in 50 ml offer closer 0.5mIU fine-tuning over 20 minute VTBIs.						

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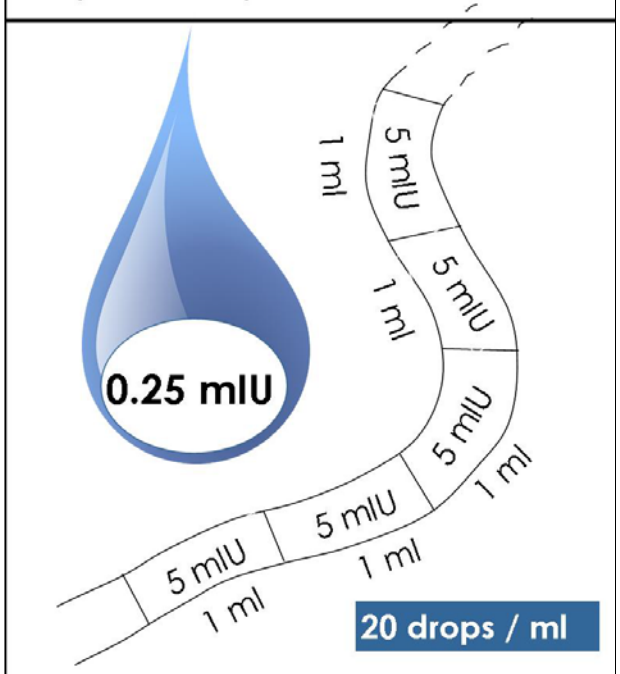
Managing synthetic oxytocin by motor-driven infusion pump

Titrate with contractions

Licensed dosage infusion rates are to be strictly limited by the evoked contractions.

Table 2 (P7) shows the mIU / ml 20-minute pump settings for 5 IU in 500 ml diluent (the standard dilution). This regime is also suitable for trial of induction of labour with a view to vaginal delivery after a previous Caesarean (necessarily without epidural), as is 2.5 IU in 500 ml (**Figure F, Table 3**) which the World Health Organisation (2017) recommends as a possible starting dilution for induction of parous women, or those in slow labour. Consider it for sensitive, young, or small women (Mansy, 2017).

Figure F (Table 3)
Synthetic Oxytocin 2.5 IU in 500 ml



Half-strength dilution for IV drip infusion, volumetric pump and syringe driver

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Table 3
2.5 IU Synthetic Oxytocin in 500 ml for drip infusion (5 mIU / ml)

0.25 mIU / drop				Total mIU / no of drops				Volume (0.05 ml / drop)			
1	2	3	4	0.25	0.5	0.75	1	0.05	0.1	0.15	0.2
5	6	7	8	**1.25**	1.5	1.75	2	**0.25**	0.3	0.35	0.4
9	**10**	11	12	2.25	**2.5**	2.75	3	0.45	**0.5**	0.55	0.6
13	14	**15**	16	3.25	3.5	**3.75**	4	0.65	0.7	**0.75**	0.8
17	18	19	**20**	4.25	4.5	4.75	**5**	0.85	0.9	0.95	**1.0**
21	22	23	24	5.25	5.5	5.75	6	1.05	1.1	1.15	1.2
25	26	27	28	**6.25**	6.5	6.75	7	**1.25**	1.3	1.35	1.4
29	**30**	31	32	7.25	**7.5**	7.75	8	1.45	**1.5**	1.55	1.6
33	34	**35**	36	8.25	8.5	**8.75**	9	1.65	1.7	**1.75**	1.8
37	38	39	**40**	9.25	9.5	9.75	**10**	1.85	1.9	1.95	**2.0**

Half-strength standard dilution in drops / mIU / ml / minute.
If IVI >10 mIU / minute, when 500 ml ends, go to 5 IU in 500 ml.

2.5 IU Synthetic Oxytocin in 500 ml for volumetric pump

mIU / minute				mIU / 20 minutes				ml / 20 minutes			
0.25	0.5	0.75	1	5	10	15	20	1	2	3	4
1.25	1.5	1.75	2	**25**	30	35	40	**5**	6	7	8
2.25	**2.5**	2.75	3	45	**50**	55	60	9	**10**	11	12
3.25	3.5	**3.75**	4	65	70	**75**	80	13	14	**15**	16
4.25	4.5	4.75	**5**	85	90	95	**100**	17	18	19	**20**
5.25	5.5	5.75	6	105	110	115	120	21	22	23	24
6.25	6.5	6.75	7	**125**	130	135	140	**25**	26	27	28
7.25	**7.5**	7.75	8	145	**150**	155	160	29	**30**	31	32
8.25	8.5	**8.75**	9	165	170	**175**	180	33	34	**35**	36
9.25	9.5	9.75	**10**	185	190	195	**200**	37	38	39	**40**

Half-strength standard dilution mIU / ml / 20 minutes.
To reduce rate by 0.25 mIU / minute slow pump by 5 mIU in 1.0 ml over 20 minutes.

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Challenges to homeostasis

When chronic fetal acidosis is already present (placental dysfunction in elevated BP in pregnancy, in fetal growth retardation and other clinical pictures), Bobrow and Soothill (1999) warn, 'anything that causes hypotension … will reduce the maternal blood supply and so oxygen delivery to the uterus'.

The mechanical lowering of BP when an epidural first takes effect has been considered an advantage to hypertensive women approaching labour, but when normotensive patients' BPs fall, plain IV fluid is rushed in to restore it. (Blood volume per kilogram body weight = 65 ml.) This takes haemodilution beyond the physiological plasma increase of 40 - 50% by term (Hytten and Paintin, 1963), adding to the cardiac stress of labour.

Myometrial hypoxia during contractions temporarily reduces oxygen to the fetus, and naturally causes physiological pain. Under epidural, repeated, unnaturally severe contraction pain due to excessive synthetic oxytocin is a profound physiological trauma, likely to lower BP from shock and acidosis.

Metabolic acidosis causes vasodilation (Salameh et al, 2014) and lower 'intracellular calcium concentration … could explain the reduction of smooth muscle tone' (Aalkjaer and Peng, 1997; Aguilar and Mitchell, 2010).

Oxytocin receptor desensitisation and vaso-dilatory influences correlate with atony after synthetic oxytocin regimes which overwork the myometrium, making PPH more likely (Brinsden and Clark, 1978).

Budden et al (2014), from their literature review, observed, 'Previous studies suggest that high-dose regimens can lead to shorter induction to delivery time and fewer failed inductions, but at the expense of increased rates of hyperstimulation and fetal distress, requiring cessation of oxytocin, caesarean section, instrumental birth, and postpartum haemorrhage'.

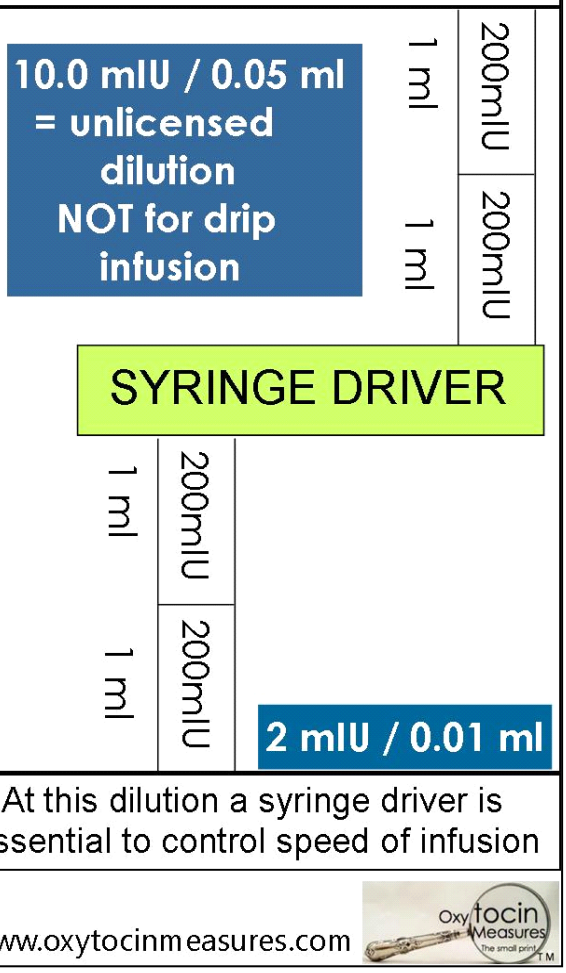
Griffiths and Campbell (2015) mention, 'Local anaesthetics can accumulate in the fetus due to 'ion trapping' if the fetus becomes acidotic … when the decreased pH in the fetus produces an increased proportion of ionised drug'.

Clearly, inhibition of maternal and fetal acidosis is clinically desirable, being favourable to sustaining individual variations in time-to-delivery.

Beazley et al (1975), analysing their comprehensive study, *Maintenance of Labour*, found 7 mIU / minute the optimum synthetic oxytocin rate, with no Caesarean sections for acidotic fetal distress (Steer et al, 1975).

'… no Caesarean sections for acidotic fetal distress'

Figure D (Table 4)
Synthetic Oxytocin 10 IU in 50 ml



At this dilution a syringe driver is essential to control speed of infusion

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Table 4
10 IU synthetic oxytocin in 50 ml diluent for Syringe Driver

mIU / minute				ml / minute			
0.5	1	1.5	2	0.0025	0.005	0.0075	0.01
2.5	3	3.5	4	**0.0125**	0.015	0.0175	0.02
4.5	**5**	5.5	6	0.0225	**0.025**	0.0275	0.03
6.5	7	**7.5**	8	0.0325	0.035	**0.0375**	0.04
8.5	9	9.5	**10**	0.0425	0.045	0.0475	**0.05**
10.5	11	11.5	12	0.0525	0.055	0.0575	0.06
12.5	13	13.5	14	**0.0625**	0.065	0.0675	0.07
14.5	**15**	15.5	16	0.0725	**0.075**	0.0775	0.08
16.5	17	**17.5**	18	0.0825	0.085	**0.0875**	0.09
18.5	19	19.5	**20**	0.0925	0.095	0.0975	**0.1**
mIU / 20 minutes				ml / 20 minutes			
10	20	30	40	0.05	0.1	0.15	0.2
50	60	70	80	**0.25**	0.3	0.35	0.4
90	**100**	110	120	0.45	**0.5**	0.55	0.6
130	140	**150**	160	0.65	0.7	**0.75**	0.8
170	180	190	**200**	0.85	0.9	0.95	**1.0**
210	220	230	240	1.05	1.1	1.15	1.2
250	260	270	280	**1.25**	1.3	1.35	1.4
290	**300**	310	320	1.45	**1.5**	1.55	1.6
330	340	**350**	360	1.65	1.7	**1.75**	1.8
370	380	390	**400**	1.85	1.9	1.95	**2.0**

To reduce rate by 0.5 mIU / minute, slow pump by 10 mIU in 0.05 ml over 20 minutes

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Managing synthetic oxytocin infusion

Synthetic oxytocin must be administered in a hospital, with one-to-one care, because known risks and unpredictable changes may demand prompt action from professionals (Novartis, 1977; Mylan, 2019; Dupont et al, 2017).

Infusion rates are *per minute* to facilitate quick correction (allaying fetal distress) if uterine relaxations after contractions last *less* than 60 seconds (Pehlivanoglu et al, 2013).

Compare the length of palpated contractions with those recorded on the tocograph trace, to factor in the discrepancy before determining whether or not to increase the synthetic oxytocin infusion rate (Bhogal, 2017).

Rate increases are guided by (not the clock) the frequency of contractions, as these prompt greater endogenous oxytocin and prostaglandins output (Vrachnis et al, 2011).

To leave the patient (professionally) unattended, please record turning off the synthetic oxytocin infusion. On return, assess, time and record: the contractions, the fetal heart (using Pinard's stethoscope), maternal pulse and BP.

If all are satisfactory, choose a slightly lower rate of synthetic oxytocin than when paused, to make way for endogenous oxytocin and enhance these contractions safely. Record the time and infusion rate after restarting, and palpate the next few contractions for strength, length and frequency.

Establishing and completing labour

Despite manufacturers warning to space increments at least 20 minutes apart, quarter-hourly changes persistently appear in trials, proven by Loscul et al (2015), to raise PPH rates.

As blood volume is related to maternal stature, an Allowable Blood Loss Estimate, if stated in case notes antenatally (36 weeks), might sharpen focus towards minimising postpartum blood loss (Manuel's Web Blood Loss Calculator, Butterworth et al, 2018).

To our knowledge, midwives in the UK work without fine-tuning options. Formal local permissions to fine-tune pump rates *downwards* during VTBI time segments are essential for improvements to PPH rates to materialise. Fine-tuning volumes vary with dilution. (eg 10 mIU / 20 minutes, **Table 2**, P7, or 5 mIU / 20 minutes, **Table 3**, P11).

To avoid oxytocin receptor desensitisation and tetanic contractions (causes of fetal distress) during the establishment of labour, fine-tune synthetic oxytocin down or up by 0.5 mIU / minute to maximise fetal oxygenation and biochemical homeostasis, so that uterine relaxations last longer than 60 seconds, to mimic relaxation between robust natural contractions, which can often last longer than 60 seconds.

Once labour is established, the infusion rate may, tentatively, be *reduced* by 0.5 mIU / minute more than once, to support the natural rhythm of only three (or maximum four) contractions in ten minutes.

Total analgesia under epidural protects the patient from pain-consciousness, but also blocks sensory information complicit with effective fetal expulsion. With Consent, epidural top-ups may be halved to allow sensation to return before pushing, for a unassisted vaginal birth.

Fitzpatrick and Walmsley (1965), estimated that expulsive contractions begin under the influence of an elevated supply of endogenous oxytocin. (From experience with the physiological dilution, it can be discontinued without compromising progress in

second stage.) Therefore, that is when to reduce the synthetic oxytocin infusion by 2 mIU - 4 mIU steps to end it prior to the birth, giving maternal oxytocin as much time as possible to adjust for third stage to achieve natural haemostasis after expulsion of the placenta.

Intramuscular Syntometrine® 1 ml will assist separation of the placenta and lessen blood loss. During the first hour after third stage, check the uterus manually, very regularly, to ensure that it is well-contracted in all cases. Or take appropriate remedial action to control bleeding.

Interpretation of the severity of impact of a woman's *excessive* blood loss is extrapolated from her Allowable Blood Loss Estimate, combined with other relevant clinical factors, to plan her postnatal support (Association of Ontario Midwives, 2017).

Figure G (Table 5)
Synthetic Oxytocin 5 IU in 50 ml

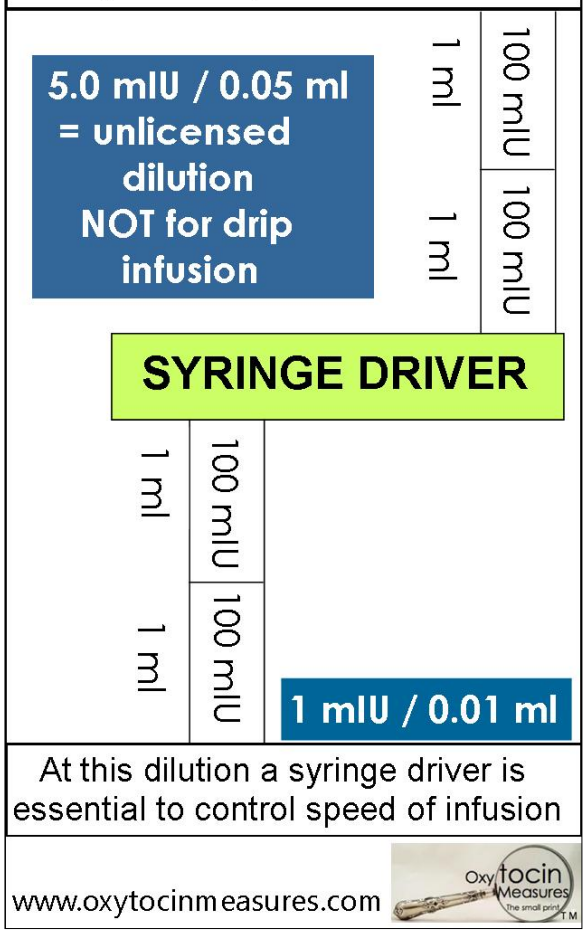

Table 5
5 IU synthetic oxytocin in 50 ml for Syringe Driver
(100 mIU per ml for administration of the licensed dosage range)

mIU / minute				ml / minute			
0.5	1	1.5	2	0.005	0.01	0.015	0.02
2.5	3	3.5	4	**0.025**	0.03	0.035	0.04
4.5	**5**	5.5	6	0.045	**0.05**	0.055	0.06
6.5	7	**7.5**	8	0.065	0.07	**0.075**	0.08
8.5	9	9.5	**10**	0.085	0.09	0.095	**0.1**
10.5	11	11.5	12	0.105	0.11	0.115	0.12
12.5	13	13.5	14	**0.125**	0.13	0.135	0.14
14.5	**15**	15.5	16	0.145	**0.15**	0.155	0.16
16.5	17	**17.5**	18	0.165	0.17	**0.175**	0.18
18.5	19	19.5	**20**	0.185	0.19	0.195	**0.2**

mIU / 20 minute				ml / 20 minute			
10	20	30	40	0.1	0.2	0.3	0.4
50	60	70	80	**0.5**	0.6	0.7	0.8
90	**100**	110	120	0.9	**1.0**	1.1	1.2
130	140	**150**	160	1.3	1.4	**1.5**	1.6
170	180	190	**200**	1.7	1.8	1.9	**2.0**
210	220	230	240	2.1	2.2	2.3	2.4
250	260	270	280	**2.5**	2.6	2.7	2.8
290	**300**	310	320	2.9	**3.0**	3.1	3.2
330	340	**350**	360	3.3	3.4	**3.5**	3.6
370	380	390	**400**	3.7	3.8	3.9	**4.0**

To reduce rate by 0.5 mIU / min, slow pump by 10 mIU in 0.1 ml over 20 minutes.

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Table 6
2.5 IU synthetic oxytocin in 50 ml for Syringe Driver
(50 mIU per ml for administration of the licensed dosage range)

mIU / minute				ml / minute			
0.5	1	1.5	2	0.01	0.02	0.03	0.04
2.5	3	3.5	4	**0.05**	0.06	0.07	0.08
4.5	**5**	5.5	6	0.09	**0.1**	0.11	0.12
6.5	7	**7.5**	8	0.13	0.14	**0.15**	0.16
8.5	9	9.5	**10**	0.17	0.18	0.99	**0.2**
10.5	11	11.5	12	0.21	0.22	0.23	0.24
12.5	13	13.5	14	**0.25**	0.26	0.27	0.28
14.5	**15**	15.5	16	0.29	**0.3**	0.31	0.32
16.5	17	**17.5**	18	0.33	0.34	**0.35**	0.36
18.5	19	19.5	**20**	0.37	0.38	0.39	**0.4**

mIU / 20 minute				ml / 20 minute			
10	20	30	40	0.2	0.4	0.6	0.8
50	60	70	80	**1.0**	1.2	1.4	1.6
90	**100**	110	120	1.8	**2.0**	2.2	2.4
130	140	**150**	160	2.6	2.8	**3.0**	3.2
170	180	190	**200**	3.4	3.6	3.8	**4.0**
210	220	230	240	4.2	4.4	4.6	4.8
250	260	270	280	**5.0**	5.2	5.4	5.6
290	**300**	310	320	5.8	**6.0**	6.2	6.4
330	340	**350**	360	6.6	6.8	**7.0**	7.2
370	380	390	**400**	7.4	7.6	7.8	**8.0**

To reduce rate by 0.5 mIU / min, slow pump by 10 mIU in 0.2 ml over 20 minutes.

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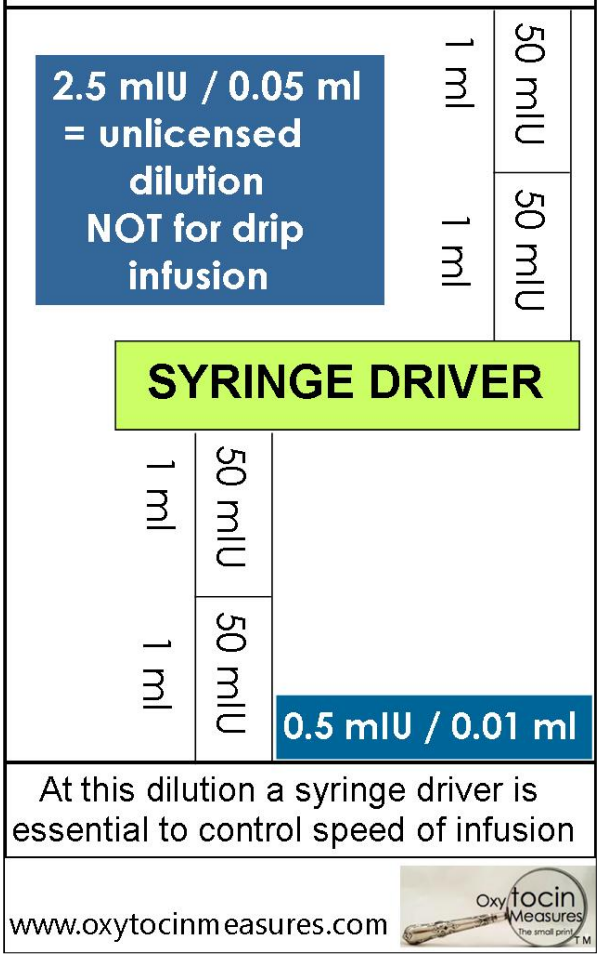
Figure H (Table 6)
Synthetic Oxytocin 2.5 IU in 50 ml



At this dilution a syringe driver is essential to control speed of infusion

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Weaker dilutions achieve greater dosage accuracy, fine-tuning flexibility and safety.

Conclusion

The body is intelligent, but is affected by its external and internal environment. The uterus has the ability to start and complete labour. We must respect and work with it, not against it.

Overall PPH rates were <7% when bovine oxytocin or synthetic oxytocin was blended as intended with endogenous oxytocin to facilitate homeostasis and maximise the efficacy of contractions. Current clinical outcomes have failed to justify two decades of unlicensed practice with synthetic oxytocin, boosting PPH rates close to 50%.

Guidelines disallow fine-tuning and are expected to be followed as 'best practice'. The midwife will be sanctioned if s/he departs from them, whereas licensed practice gives the physiologically beneficial flexibility to adjust synthetic oxytocin up, down, stabilise or stop.

Once upon a time, low PPH rates were admired and coveted, but the 2001 change in synthetic oxytocin practice has not been undertaken with a readiness to reverse it, if proving detrimental to the ladies. The RCOG's advice removed too many infusion rates for meaningfully individualised care to be given (**Figure B**, P4).

It does not take into enough consideration reasons for varying levels of sensitivity to synthetic oxytocin, nor spontaneous endogenous oxytocin release.

Valid informed Consent should be courted for the licensed dilution (and increment limits) or half-strength synthetic oxytocin dilution, because optimally titrated, both are clinically effective to enhance, induce, and support as natural a labour as possible, and they significantly mitigate known pump error-factor slippage, that varies with synthetic oxytocin dilutions and each unique infusion device.

We are confident that without harm - or further research - licensed practice with synthetic oxytocin could be re-introduced to improve women's experience of labour, diminish PPH rates and maternal morbidity (more) naturally, and bring notable improvements to fetal outcomes.

The challenges to administering synthetic oxytocin arising from unlicensed dilutions and increments, and variations in pump accuracy, are **all solved by fine-tuning** 0.5 mIU at a time of the licensed dilution - 5 IU in 500 ml - using the lowest effective dosage rate of forty available to support homeostasis, **with the contractions and maternal oxytocin**.

Postscript

Synthetic oxytocin concentrate was designed to be used copiously diluted to bring its dilution close to the natural hormone, oxytocin. Modern research indicates that peripheral oxytocin is not much affected by intravenous treatment, as natural hormones are all released directly into the bloodstream, taking less than a minute to reach their target organ. Synthetic oxytocin is metabolised within 3 minutes.

The importance of oxytocin receptor sensitivity, and the conscious avoidance of desensitising them with too strong or too fast an infusion, cannot be overstated, as mismanagement of the infusion leads to tetanic contractions, and possibly a fetal response to oxytocin, as well as hostile hypoxia - all apart from the concerns for which synthetic oxytocin is being used (to induce or enhance uterine contractions).

When the licensed dilution is used, an accidental bolus of 0.5 or 0.6 ml (5 mIU or 6 mIU) is insignificant compared with the same volume of unlicensed strengths, which, Theobald noted, may cause 'fetal heart irregularities'. It is safe, therefore, to leave the bolus function accessible **as long as it is not a button on the outside of the device which can be leaned upon by accident or with malicious intent**.

Post postscript

In 2015 we approached Novartis with a question.

If - as is being practised - it is safe to use Syntocinon in an unlicensed manner, why has the licence not been updated to reflect this?

After a few infrequent exchanges we asked Novartis for a statement.
Novartis replied 16 January 2018 and gave us permission to quote:

'Novartis only recommend use of the licensed dosage and method of administration, as detailed in the Syntocinon Summary of Product Characteristics (SmPC). We cannot advocate and do not recommend use of any product in an unlicensed manner.'

During this period, Novartis negotiated with Mylan to take over the brand 'Syntocinon' in 2019. https://www.medicines.org.uk/emc/product/9736/smpc

Patient Information Leaflet by Mylan (April 2022)
https://www.medicines.org.uk/emc/files/pil.9735.pdf

6.1 List of excipients: Sodium acetate tri-hydrate, acetic acid, chlorobutanol, ethanol and water for injections.

We are to assume that in the licensed dilutions, the negative effects of chlorobutanol (aka chlorbutol) and ethanol are sufficiently mitigated.

All other manufacturers of synthetic oxytocin for intravenous infusion contain no chlorobutanol and no ethanol. The instructions for use in induction of labour are the same in all the SmPC leaflets.

References

Aalkjaer C, Peng HL. pH and smooth muscle. Acta Physiologica Scandinavica. 1997;161(4):557–66 https://www.ncbi.nlm.nih.gov/pubmed/9429665 doi:10.1046/j.1365-201X.1997.00263.x

Aguilar HN, Mitchell BF. Physiological pathways and molecular mechanisms regulating uterine contractility. Human Reproduction Update. June, 2010;16(6):725–744 https://doi.org/10.1093/humupd/dmq016 https://academic.oup.com/humupd/article/16/6/725/740554

Archer JR. Points from letters: Synthetic Oxytocin. British Medical Journal. July, 1969;3(5664):242 (Letter) https://www.bmj.com/content/3/5664/242.5 doi: https://doi.org/10.1136/bmj.3.5664.242-d

Association of Ontario Midwives. Life After Postpartum Haemorrhage: Recovering from the Unexpected. 2017. (Copy and paste this URL) https://www.ontariomidwives.ca/sites/default/files/CPG%20client%20resources/Life-after-PPH-English.pdf **(multilingual)** https://www.ontariomidwives.ca/client-handouts

Barley SL, Ripman HA. Induction of labour with synthetic oxytocin. British Medical Journal. 1970;4(5726):55–56 (Letter) https://www.bmj.com/content/4/5726/55.3 https://www.bmj.com/content/4/5726/56.3 **(diagram of method)**

Beazley JM, Bamovic I, Feld MS. Maintenance of labour. British Medical Journal. 1975;2(5965):248-250 https://doi.org/10.1136/bmj.2.5965.248 https://www.bmj.com/content/bmj/2/5965/248.full.pdf

Berde B. Some observations on the circulatory effects of oxytocin, vasopressin and similar polypeptides. In: Pinkerton JHM (ed). Advances in Oxytocin Research. London: Pergammon Press Ltd; 1965

Beynon CL. The normal second stage of labour: a plea for reform in its conduct. The Journal of Obstetrics and Gynaecology of the British Empire. December 1957;64(6):815-20 doi: 10.1111/j.1471-0528.1957.tb08483.x. https://obgyn.onlinelibrary.wiley.com/doi/10.1111/j.1471-0528.1957.tb08483.x

Bhogal K. Focus on cardiotocography: Intrapartum monitoring of uterine contractions. British Journal of Midwifery. 2017;25(8):491–497 https://www.magonlinelibrary.com/doi/abs/10.12968/bjom.2017.25.8.491

Birthrights UK Protecting human rights in childbirth. Factsheet on Consent. https://www.birthrights.org.uk/factsheets/consenting-to-treatment/

Bobrow CS, Soothill PW. Causes and consequences of fetal acidosis. Archives of Disease in Childhood - Fetal and Neonatal Edition. 1999;80: F246-F249 http://dx.doi.org/10.1136/fn.80.3.F246 https://fn.bmj.com/content/fetalneonatal/80/3/F246.full.pdf

Brinsden PRS, Clark AD. Postpartum Haemorrhage after induced and spontaneous labour. British Medical Journal. September, 1978;2(6141):855–856 https://doi.org/10.1136/bmj.2.6141.855 https://www.bmj.com/content/bmj/2/6141/855.full.pdf

Brinsden PR, Clark AD. Postpartum haemorrhage and induction of labour. British Medical Journal. 1979;1(6171):1147 (Letter) https://www.bmj.com/content/1/6171/1147.3 https://doi.org/10.1136/bmj.1.6171.1147-b

British National Formulary. Oxytocin. 2021. https://bnf.nice.org.uk/drug/oxytocin.html

Brown DB. Syntometrine. British Medical Journal. 1962;2(5307):797 (Letter) https://www.bmj.com/content/2/5307/797.1 https://doi.org/10.1136/bmj.2.5307.797

Brown DB. Oxytocic drugs in labour. British Medical Journal. 1968;1(5591):578 (Letter) https://doi.org/10.1136/bmj.1.5591.578 https://www.bmj.com/content/1/5591/578.1

Budden A, Chen LJY, Henry A. High-dose versus low-dose oxytocin infusion regimens for induction of labour at term. Cochrane Database of Systematic Reviews. 2014 https://doi.org/10.1002/14651858.CD009701.pub2 https://www.cochranelibrary.com/cdsr/doi/10.1002/14651858.CD009701.pub2/full

Butterworth JF Mackey DC, Wasnick JD. Fluid management and blood component therapy. In: Butterworth JF, Mackey DC, Wasnick JD (eds). Morgan

and Mikhail's Clinical Anesthesiology, 6th edition. Ohio: McGraw-Hill Education; 2018

Chukudebelu WO, Marshall AT, Chalmers JA. Use of "Syntometrine" in the third stage of labour. British Medical Journal. May, 1963;1(5342):1390–1391 https://www.bmj.com/content/1/5342/1390 https://www.bmj.com/content/1/5342/1391 https://doi.org/10.1136/bmj.1.5342.1390

Coltart TH, Nash TG. Pitocin buccal in late pregnancy. British Medical Journal. 1974; 3(5928):467 (Letter) https://doi.org/10.1136/bmj.3.5928.467 https://www.bmj.com/content/3/5928/467.1

Dawood MY. Novel approach to oxytocin induction-augmentation of labor: application of oxytocin physiology during pregnancy. Advances in Experimental Medicine and Biology. 1996;395:585–594. https://europepmc.org/article/med/8714022

Dupont C, Carayol M, Le Ray C et al. Oxytocin administration during spontaneous labour: guidelines for clinical practice. Gynécologie, obstétrique, fertilité & sénologie, Fédération nationale des collèges de gynécologie médicale. 2017 Jan;45(1):56–61 doi:10.1016/j.gofs.2016.12.017 https://www.ncbi.nlm.nih.gov/pubmed/28238320

Ebirim LM, Buowari OY, Ghosh S. Physical and psychological aspects of pain in obstetrics. (Chapter 9, Page 40395) In: Subhamay Ghosh (ed). Pain in Perspective. IntechOpen Book Series. 2012. doi: 10.5772/2627 https://www.intechopen.com/books/2238 ISBN978-953-51-0807-8. eBook (PDF) ISBN978-953-51-7037-2

Embrey MP, Barber DTC, Scudamore JH. Use of "syntometrine" in prevention of post-partum haemorrhage. British Medical Journal. 1963;1(5342):1387 (Letter) https://www.bmj.com/content/1/5342/1387 https://doi.org/10.1136/bmj.1.5342.1387

EVER Valinject GmbH / Kent Pharma UK Ltd 22.06.2018 https://www.medicines.org.uk/emc/product/12689/smpc (5 IU) https://www.medicines.org.uk/emc/product/12690/smpc (10 IU)

Feeney JG. Water intoxication and oxytocin. British Medical Journal *(Cl Res Ed)* July, 1982;285:243 https://www.bmj.com/content/285/6337/243

https://doi.org/10.1136/bmj.285.6337.243

Fitzpatrick RJ, Walmsley CF. The release of oxytocin during parturition. (P 51), P 67, Fig 7 (Graph modified from Coch et al (1964)) In: Pinkerton JHM (ed). Advances in oxytocin research. London: Pergamon Press Ltd; 1965. eBook ISBN: 9781483156507

Ford JB, Roberts CL, Simpson JM et al. Increased postpartum hemorrhage rates in Australia. International Journal of Gynecology and Obstetrics. October, 2007;98(3):237–43 doi:10.1016/j.ijgo.2007.03.011 https://www.researchgate.net/publication/6349581_Increased_postpartum_hemorrhage_rates_in_Australiaa

Griffiths SK, Campbell JP. Placental structure, function and drug transfer. British Journal of Anaesthesia: Continuing Education in Anaesthesia Critical Care & Pain. May, 2015;15(2):84–89 https://doi.org/10.1093/bjaceaccp/mku013 https://academic.oup.com/bjaed/article/15/2/84/248526

Hofmeyr G, Abdel-Aleem H, Abdel-Aleem MA. Uterine massage for preventing postpartum haemorrhage. Cochrane Database of Systematic Reviews 2013 https://pubmed.ncbi.nlm.nih.gov/23818022/ https://www.cochranelibrary.com/cdsr/doi/10.1002/14651858.CD006431.pub3/full doi:10.1002/14651858.CD006431.pub3

Hytten FE, Paintin DB. Increase in plasma volume during normal pregnancy. International Journal of Obstetrics and Gynaecology. 1963;70(3):402–407 https://obgyn.Onlinelibrary.wiley.com/doi/pdf/10.1111/j.1471-0528.1963.tb04922.x https://doi.org/10.1111/j.1471-0528.1963.tb04922.x

JHP Pharmaceuticals. Pitocin Archived. 2009. https://dailymed.nlm.nih.gov/dailymed/archives/fdaDrugInfo.cfm?archiveid=10055

Kemp J. Clinical trial of "Syntometrine" in the third stage of labour. British Medical Journal. 1963;1(5342):1391 (Letter) https://www.bmj.com/content/1/5342/1391 **and** https://www.bmj.com/content/1/5342/1392 https://doi.org/10.1136/bmj.1.5342.1391 **and** https://doi.org/10.1136/bmj.1.5342.1392

Kent Pharma Ltd. Oxytocin 10 IU solution for injection. 2018.

https://www.medicines.org.uk/emc/product/12690/smpc#gref

Knight M, Callahan WM, Berg C et al. Trends in postpartum hemorrhage in high resource countries: a review and recommendations from the International Postpartum Hemorrhage Collaborative Group. British Medical Journal. BMC Pregnancy & Childbirth. 2009;9:55 https://doi.org/10.1186/1471-2393-9-55 https://bmcpregnancychildbirth.biomedcentral.com/articles/10.1186/1471-2393-9-55#Bib1

Loscul C, Chantry AA, Caubit L et al. Association between oxytocin augmentation intervals and the risk of postpartum haemorrhage. Journal de Gynécologie Obstétrique et Biologie de la Reproduction. 2015;45(7):708–15 http://europepmc.org/article/MED/26874663 doi: 10.1016/j.jgyn.2015.12.005 **(French)** https://dumas.ccsd.cnrs.fr/dumas-00874294/document

Lutomski JE, Byrne BM, Devane D et al (2012). 'Increasing trends in atonic postpartum haemorrhage in Ireland: an 11-year population-based cohort study'. British Journal of Obstetrics and Gynaecology, February, 119(3):306-14. https://obgyn.onlinelibrary.wiley.com/doi/10.1111/j.1471-0528.2011.03198.x doi/10.1111/j.1471-0528.2011.03198.x

Mansy A. Does labor augmentation with oxytocin increase the risk of postpartum hemorrhage? A randomized controlled trial. Clinics in Mother and Child Health. 2017;14:268 https://www.walshmedicalmedia.com/open-access/does-labor-augmentation-with-oxytocin-increase-the-risk-of-postpartumhemorrhage-a-randomized-controlled-trial-2090-7214-1000268.pdf

Manuelsweb.com. Manuel's web allowable blood loss calculator. 2017. https://www.manuelsweb.com/blood_loss.htm

MacKenzie IZ, Castle B, Bellinger J. Transfer of prostaglandins to the fetus after prostaglandin E2 vaginal pessary administration. American Journal of Obstetrics and Gynaecology. 1989;161(4):920–923 https://doi.org/10.1016/0002-9378(89)90752-7

Moodie JE, Moir DD. Ergometrine, Oxytocin, and Extradural Analgesia. British Journal of Anaesthesia. 1976;48:571 https://www.bjanaesthesia.org.uk/article/S0007-0912(17)48663-6/pdf

Mylan Products Ltd. Syntocinon 5 IU. 2019. (accessed 1 September 2021) https://www.medicines.org.uk/emc/product/9736/smpc

NHS Digital. NHS Maternity Statistics, England 2016 - 2017. HES NHS Maternity Statistics Tables, Index - Table 7b, Delivery Complications, Table 7a, **Postpartum Haemorrhage**
https://digital.nhs.uk/data-and- information/publications/statistical/nhs-maternity-statistics/**2016-17** **17.66%**
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Normington EAM. A Simplified method of syntocinon infusion following amniotomy. The Journal of Obstetrics and Gynaecology of the British Commonwealth. 1972;79(12):1108–1112
https://doi.org/10.1111/j.1471-0528.1972.tb11895.x

Nursing and Midwifery Council. The Code. Professional Standards of Practice and Behaviour for Nurses, Midwives and Nursing Associates. 2018.
https://www.nmc.org.uk/standards/code/

Oxytocinmeasures.com. Synthetic Oxytocin Figures, Graphics and Tables. 2021. www.oxytocinmeasures.com/downloads

O'Driscoll K, Jackson RJA, Gallagher JT. Prevention of prolonged labour. British Medical Journal. 1969;2(5655):477–480 doi:10.1136/bmj.2.5655.477
https://www.bmj.com/content/bmj/2/5655/477.full.pdf

Patterson JH. Third stage of labour. British Medical Journal. 1964;1(5379):377 (Letter) https://doi.org/10.1136/bmj.1.5379.377-d
https://www.bmj.com/content/1/5379/377.5

Pehlivanoglu B, Bayrak S, Dogan M. A close look at the contraction and relaxation of the myometrium; the role of calcium. Journal Of The Turkish-German Gynecological Association. 2013;14(4):230–234
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3935537/
doi:10.5152/jtgga.2013.67763

Pinkerton JHM. Buccal Oxytocin. British Medical Journal. 1964;2(5421):1393 (Letter) https://doi.org/10.1136/bmj.2.5421.1393 https://www.bmj.com/content/2/5421/1393.1

Pinkerton JHM. Some observations on the circulatory effects of oxytocin, vasopressin and similar polypeptides. Discussion - P34 In: Pinkerton JHM (ed). Advances in Oxytocin Research. London: Pergammon Press Ltd; 1965. ebook. ISBN: 9781483156507

Quinn MJ. Rising rate of haemorrhage in the UK. British Medical Journal. 2014;349:g4984 http://www.bmj.com/content/349/bmj.g4984/rr/763489

Rodeck CH. Geoffrey William Theobald (1896–1977). JLL Bulletin: Commentaries on the history of treatment evaluation https://www.jameslindlibrary.org/articles/geoffrey-william-theobald-1896-1977/

Royal College of Obstetrics and Gynaecologists. Induction of labour. RCOG evidence-based clinical guidelines. June 2001. ISBN 1-900364-50-6 http://www.perinatal.sld.cu/docs/guiasclinicas/inductionoflabour.pdf

Royal College of Obstetricians and Gynaecologists. (National Collaborating Centre for Women's and Children's Health) Induction of Labour, Revision of 2001 guidance July, 2008. Appendix D, Table D.2 Footnote b. https://www.nice.org.uk/guidance/ng207/evidence/full-guideline-july-2008-pdf-9266823757 ISBN-13: 978-1-904752-48-6

Royal College of Obstetrics and Gynaecologists. Heavy bleeding after birth (postpartum haemorrhage). 2016. https://www.rcog.org.uk/en/patients/patient-leaflets/heavy-bleeding-after-birth-postpartum-haemorrhage/

Salameh AI, Ruffin VA, Boron WF. Effects of metabolic acidosis on intracellular pH responses in multiple cell types. The American Journal of Physiology Regulatory, Integrative and Comparative Physiology. 2014;307(12):R1413-1427 doi: 10.1152/ajpregu.00154.2014 https://www.physiology.org/doi/full/10.1152/ajpregu.00154.2014 https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4269672/ https://www.ncbi.nlm.nih.gov/pubmed/25209413

Stallworthy J. A Plea for the freer use of blood transfusion in obstetrics. British Medical Journal. January, 1939;1(4073):153 (Letter)
https://doi.org/10.1136/bmj.1.4073.153
https://www.bmj.com/content/1/4073/153

Steer PJ, Little DJ, Lewis NL et al. Uterine activity in induced labour. International Journal for Obstetrics and Gynaecology. 1975;82(6):433–441
https://obgyn.onlinelibrary.wiley.com/doi/abs/10.1111/j.1471-0528.1975.tb00666.x

Svanstrom MC, Biber B, Hanes B et al. Signs of myocardial ischaemia after injection of oxytocin: a randomized double-blind comparison of oxytocin and methyl-ergometrine during Caesarean section. British Journal of Anaesthesia. 2008;100(5):683–689 https://academic.oup.com/bja/article/100/5/683/227825
https://www.bjanaesthesia.org/article/S0007-0912(17)34337-4/fulltext
https://doi.org/10.1093/bja/aen071

Theobald GW, Graham A, Campbell BJ et al. The use of post-pituitary extract in physiological amounts in obstetrics. A preliminary report. British Medical Journal. 1948;2(4567):123–127 https://doi.org/10.1136/bmj.2.4567.123
https://www.bmj.com/content/2/4567/123

Theobald GW, Kelsey HA, Muirhead JMB. The pitocin drip. The Journal of Obstetrics and Gynaecology of the British Empire. October, 1956 Vol LXIII No 5
https://obgyn.onlinelibrary.wiley.com/doi/abs/10.1111/j.1471-0528.1956.tb05543.x

Theobald GW. Home on the second day: the Bradford experiment. British Medical Journal. December, 1959;2(5163):1364–1367
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC1990899

Theobald GW. The separate release of oxytocin and antidiuretic hormone. Journal of Physiology. 1959 Dec;149(3):443–461.
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC1363253/ (full)
doi: 10.1113/jphysiol.1959.sp006351 In: Caldeyro-Barcia R, Heller H. (eds). Oxytocin: Proceedings of an International Symposium held in Montevideo, 1959. Oxford. Pergamon Press; 1961.

Theobald GW. Buccal Oxytocin. British Medical Journal. 1965;1(5428):190–192 (Letter) https://www.bmj.com/content/1/5428/190.5 **and**
https://www.bmj.com/content/1/5428/191.5

Theobald GW. Induction of labour with buccal oxytocin. British Medical Journal. 1966a;1(5501):1479 (Letter) http://www.bmj.com/content/1/5501/1479.2

Theobald GW. Buccal oxytocin. British Medical Journal. 1966b;2(5514):645–646 (Letter) https://www.bmj.com/content/2/5514/645.5 **and** https://www.bmj.com/content/2/5514/646.5

Thompson JF, Heal LJ, Roberts CL, Ellwood DA. Women's breastfeeding experiences following a significant primary postpartum haemorrhage: A multicentre cohort study. International Breastfeeding Journal. 2010:5:5 https://internationalbreastfeedingjournal.biomedcentral.com/articles/10.1186/1746-4358-5-5 **2** https://doi.org/10.1186/1746-4358-5-5 **3** https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2889881/

Tracy SK, Tracy MB. Costing the cascade: estimating the cost of increased obstetric intervention in childbirth using population data. International Journal of Obstetrics and Gynaecology, August 2003, 110(8):717–724 https://doi.org/10.1111/j.1471-0528.2003.02045.x

Turnbull AC, Anderson AB. Induction of labour. II. Intravenous oxytocin infusion. The Journal of Obstetrics and Gynaecology of the British Empire. 1968 Jan;75(1):24–31 https://www.ncbi.nlm.nih.gov/pubmed/5635241 doi:10.1111/j.14710528.1968.tb00116.x.

Vigneaud V, Ressler C, Trippett S et al. The synthesis of an octapeptide amide with the hormonal activity of oxytocin, Journal of Biological Chemistry 1953;205(2):949–957 http://www.jbc.org/content/205/2/949.full.pdf

Vrachnis N, Malamas FM, Stavros S et al. The oxytocin-oxytocin receptor system and its antagonists as tocolytic agents. International Journal of Endocrinology. 2011;2011:350546 Open Access online at https://www.hindawi.com/journals/ije/2011/350546/ Cited by Melmed S, Polonsky K S, Larsen P R and Kronenberg H M (2016). In: Williams Textbook of Endocrinology, 13th edition. Philadelphia. Saunders. Posterior Pituitary, p 325, reference 280, listed p 332. http://dx.doi.org/10.1155/2011/350546

Walsh D. Pain and epidural use in normal childbirth. Evidence Based Midwifery. 2009;7(3):89-93 (Zepherina Veitch Memorial Lecture) http://activebirthpools.com/wp-content/uploads/2014/05/Pain-and-epidural-use-in-normal-childbirth.pdf

Weeks A, Neilson J. Rethinking our approach to postpartum haemorrhage and uterotonics. British Medical Journal. 2015;351:h3251 https://livrepository.liverpool.ac.uk/2047825/1/Weeks%20Neilson%20BMJ%202015%20351%20h3251.pdf https://doi.org/10.1136/bmj.h3251

Weeks A, Cunningham C, Taylor W et al. A phase 2 clinical trial of the PPH Butterfly, a new device to 'turn off the tap' of Post-Partum Hemorrhage. Authorea. 2021 https://doi.org/10.22541/au.162015824.47500455/v1

World Health Organisation. 2010. Oxytocin: Adopted Text for the International Pharmacopoeia (Requirements, p2) www.who.int/medicines/publications/pharmacopoeia/Oxytocin-mono_QAS07241FINALJune10.pdf

World Health Organization. Managing complications in pregnancy and childbirth: a guide for midwives and doctors, 2nd edition. 2017. 2nd edition. Geneva. Licence: CC BY-NC-SA 3.0 IGO. ISBN**:** 9789241565493. Free Download 4.9 MB. [P-24, p356 of 492] https://www.who.int/publications/i/item/9789241565493

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