Postpartum Haemorrhage and Synthetic Oxytocin Dilutions in Labour

By **Monica Tolofari,** *Consultant Midwife*

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Abstract

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

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

Unlicensed SO dilutions and increments, desensitising of oxytocin receptors (OTRs) and unmeasured error factors in infusion pumps, affect labour outcomes and PPH rates.

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

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

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

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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, 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 express informed consent from women for any unlicensed synthetic oxytocin practices.

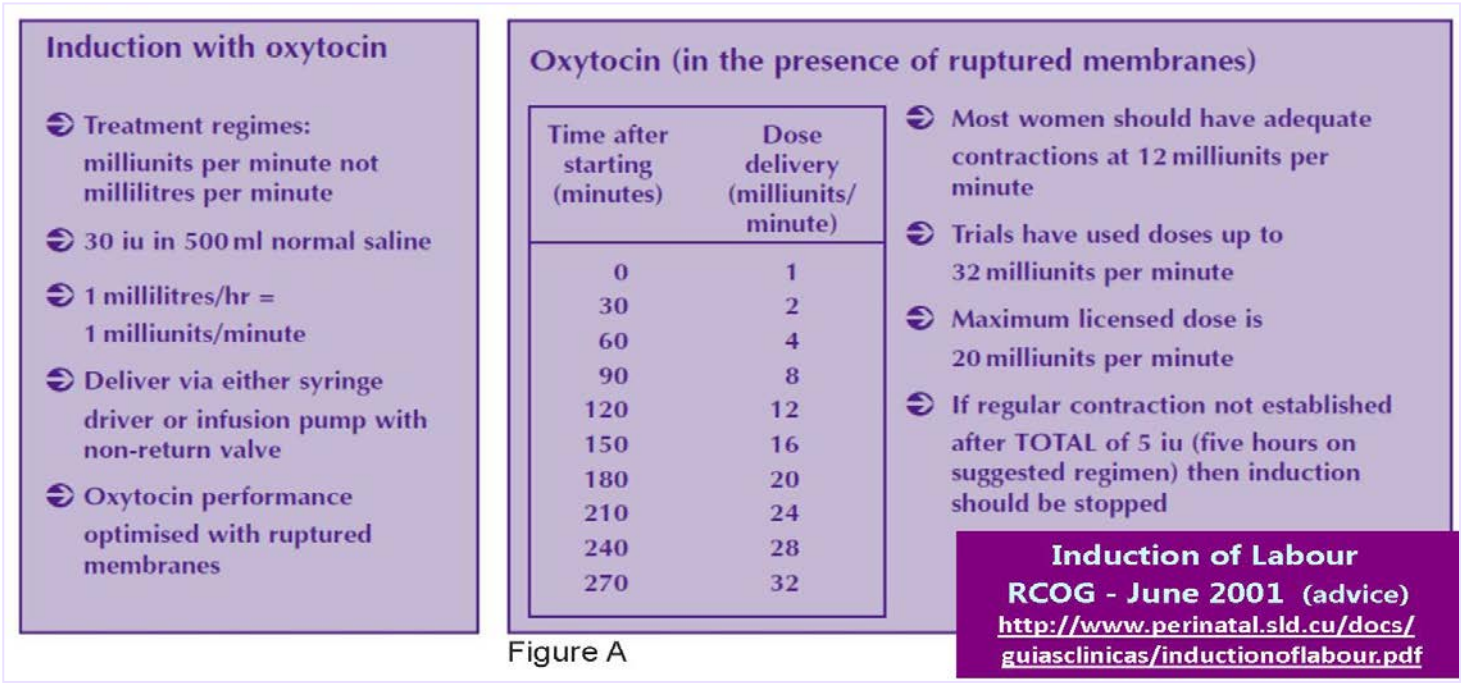

Figure A

Methodology

We reviewed key research before and after SO (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 SO 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. *[Find NHS Digital in Citations. Links to overall PPH rates.]*

We sent a freedom-of-information (FOI) request to all UK maternity units (2019), re questing their infusion devices, SO regimes and blood loss statistics.

Key findings of FOI

- >90% of induction of labour / SO 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%

Other findings

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

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

Standard pump error factors came to our attention.

From the literature search, we noted:

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

Bovine post-pituitary extract was used prior to SO (Theobald et al, 1948).

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

1960s - PPH fatalities

Berde (1965) comments that obstetricians calculate bovine oxytocin / SO on '1 mg = 450,000 milliunits'. He observed moderate lowering of blood pressure (BP) after experimental pharmacological doses of SO, 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 category.

Respecting this 'powerful hormone' (Theobald June & Sept, 1966), we strongly advocate that the full 'recommended dosage range' be re-embedded in local SO 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 <u>patient</u> to draw attention to the status of a (healthy) pregnant woman now receiving SO infusion, <u>changing from *normal*</u> to ***highly-dependent obstetric care*** due to the risks of SO 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 (Walsh, 2009, Tracy and Tracy, 2003).

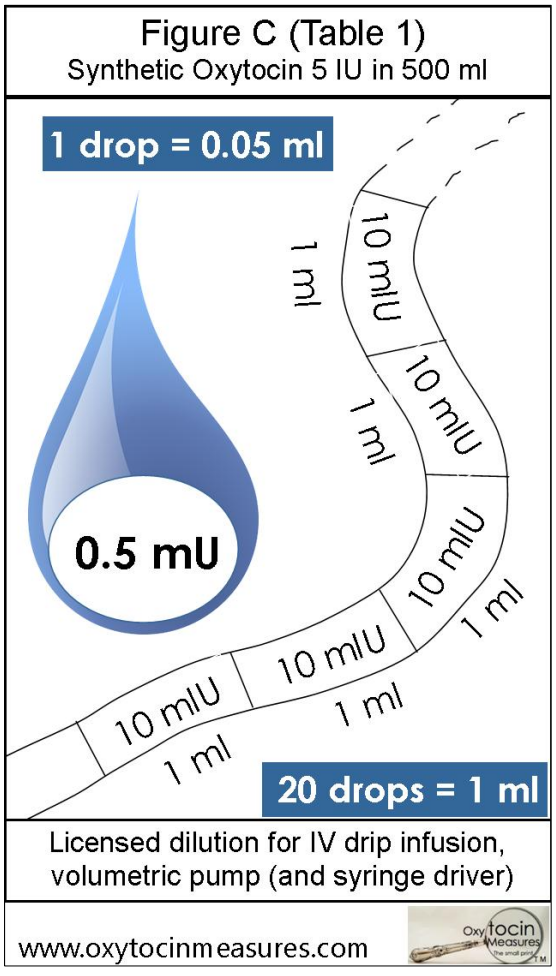
Calibration of synthetic oxytocin for intravenous infusion

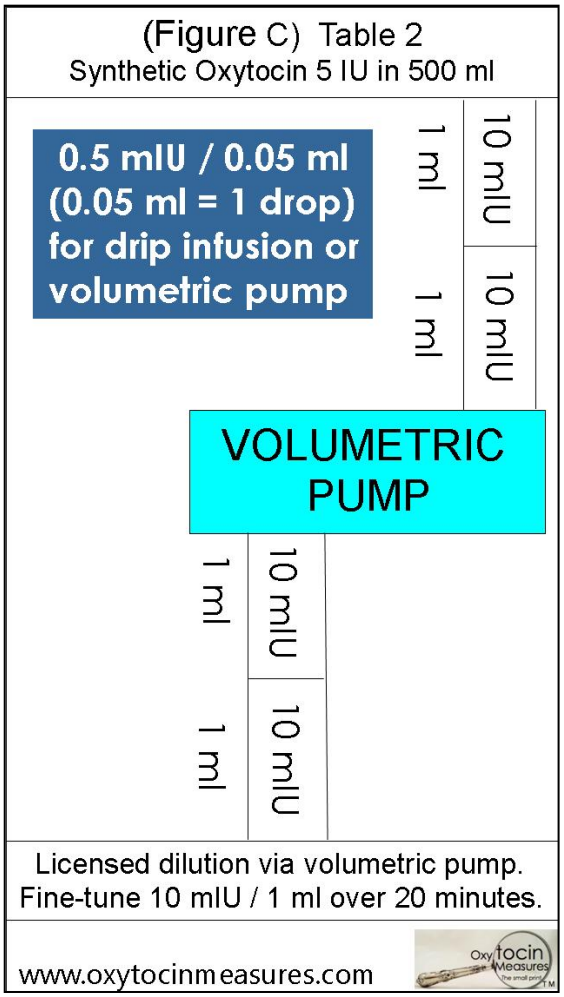
Synthetic oxytocin by weight

- International Units (IU) define organic (bio-) chemicals.
- 1 mg SO = 600 IU biological activity (World Health Organization (WHO) 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** below, **Table 1,** P7, **Table 2**, P8**)**





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

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

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

Tools

1 ml = 20 drops

1 IU = 1,000 mIU

[Decimal notation] ∴ 1 drop contains 0.5 mIU SO (See SPC).

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

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

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

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

Licensed dilution SO in mIU, in drops / minute, mIU/drop and millilitres (ml).
A 1 drop - 20 drops / minute **B** 21 drops - 40 drops / minute

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Table 2
(mIU / 1 and 20 minutes / 20 minute VTBI ml)
5 IU SO 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 SO 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-SO 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 - if 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 motorised, variable-speed infusion pump' if possible.

Dilution

We use the word dilution when SO 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.

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

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

Table 1 [above] 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.

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

All unlicensed practices oblige clinical justification and to obtain valid, informed, patient Consent.

Unlicensed practices

- **Any intramuscular injection >5 IU** - 10 IU, and 20 IU or 30 IU in theatre post-Caesarean (Svanstrom et al, 2008).
- **SO 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,** P5**)**, an experienced obstetrician should examine the patient for clinical indications for this new unlicensed treatment. **The dose must be separately prescribed to proceed**.

Unlicensed synthetic oxytocin usage after labour

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

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

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

De-sensitisation of oxytocin receptors

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

Can too much SO block the release of natural oxytocin?

He said:

'… If you give too much oxytocin [SO] when the uterus is fully ready – when there are lots of receptors [OTRs] – 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.

Volumetric pumps ± 5% to ±10% at very slow rates. Syringe Drivers ± 2%. Each pump at its best has a unique, inbuilt error factor, which, since SO causes pain, adds another cause for caution to SO administration, and fine-tuning with contractions.

The stronger the SO concentration, the higher the mIU in the smallest volumes (after the decimal point) for VTBI.

10 IU in 1 ml SO 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,** P14**)**. Consider 5 IU in 50 ml instead **(Table 5,** P17**). (Table 6** (2.5 IU in 50 ml) P18**)**

In volumetric pumps, slow VTBIs militate against unlicensed concentrations where VTBI times would be lengthened to attempt fine-tuning (as the error factor rises).

Managing SO by motorised infusion pump

Disable the bolus function

Motorised infusion devices vary, so it is important to comply with each one's specific operational routines and limitations to administer SO safely **(Figure E - Table of Dilutions).** On the pump, or in its software, the bolus option should be disabled permanently or routinely prior to SO 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.)

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
Drip Infusion	500	2.5	2,500	5	Half-strength	Table 3
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
Syringe Driver	49.5	2.5	2,500	50	0.5 mIU/0.01 ml	Table 6
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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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.
If IVI >10 mIU / minute, when 500 ml ends, go to 5 IU in 500 ml

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Titrate with contractions

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

Table 2 (P8) shows the mIU / ml, 20-minute pump settings for 5 IU in 500 ml diluent (the standard dilution). This regime is suitable for trial of SO infusion [and treatment after previous Caesarean section], as is 2.5 IU SO in 500 ml **(Table 3** above**),** which WHO (2017) recommend as a possible starting dilution. Consider half-strength dilutions for: sensitive, parous, young, or small women (Mansy, 2017).

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 SO is a profound physiological trauma, likely to lower BP from shock and acidosis. [Note - this paragraph was changed a bit.]

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).

OTR desensitisation, and vaso-dilatory influences correlate with atony after SO 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 SO rate, with no Caesarean sections for acidotic fetal distress (Steer et al, 1975).

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

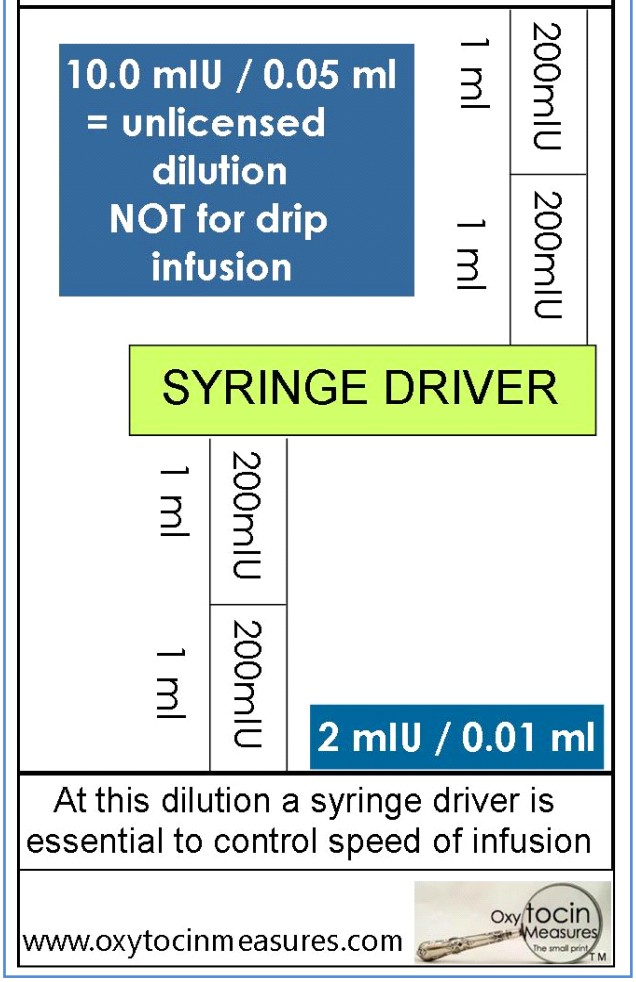

Table 4
10 IU synthetic oxytocin in 50 ml diluent for Syringe Driver

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

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Managing synthetic oxytocin infusion

SO 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 SO infusion rate (Bhogal, 2017).

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

To leave the patient (professionally) unattended, please record turning off the SO 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 SO 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 (eg 10 mIU / 20 minutes, **Table 2,** or 5 mIU / 20 minutes, **Table 3**). [Fine-tuning volumes vary with dilution.]

To avoid OTR desensitisation and tetanic contractions (causes of fetal distress) during the establishment of labour, fine-tune SO down or up by 0.5 mIU / minute as

indicated by uterine relaxations lasting longer than 60 seconds, to maximise fetal oxygenation and biochemical homeostasis.

Robust natural contractions 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 physiological SO dilution, it can be discontinued without compromising progress in second stage. Therefore, that is when to reduce the SO 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. [Useful citations were added here.]

Dosage accuracy, safety and ease of titration with contractions, all increase with weaker dilutions

The **Conclusion** follows **Table 5** for 5 IU in 50 ml (100 mIU/ml - 10 times the licensed dilution) and **Table 6** for 2.5 IU in 50 ml (50 mIU/ml - 5 times the licensed dilution) for syringe drivers, for more accurate dosage calculation. [And for easier fine-tuning.]

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

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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 min

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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 SO 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 SO, 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 SO up, down, stabilise or stop.

Once upon a time, low PPH rates were admired and coveted, but the 2001 change in SO 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, P5).

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

Valid informed Consent should be courted for the licensed dilution (and increment limits) or half-strength SO 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 SO dilutions and each unique infusion device.

We are confident that without harm - or further research - licensed practice with SO 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.

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

Email: admin@oxytocinmeasures.com **(or use our contact form).**

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https://digital.nhs.uk/data-and-information/publications/statistical/nhs-maternity-statistics/2018-19 **20.63%**

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