Newson Health
Menopause & Wellbeing Centre

Oestradiol Audit

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Introduction

This study seeks to assess the correlation between serum oestradiol level and transdermal oestrogen dose, the relationship between oestradiol levels and menopause symptom scores, and whether serum oestradiol level is predicative of the likelihood of abnormal uterine bleeding (AUB). Specifically, the study explores the risk of problematic bleeding in women on higher doses of transdermal oestrogen (TDE) vs women on lower doses.

Materials and methods

Serum oestradiol levels conducted via the lab used by Newson Health were collected from the dates of August 2021 to August 2022. Only data from patients who were using TDE were included. Further relevant clinical information was collected from each patient's clinical notes including the type & dose of HRT they were taking (both TDE & the endometrial protection being used), whether they had AUB or not and if so, the findings of their ultrasound imaging +/- biopsy results as well as their MSQ score at the time.

A total 348 patients' oestradiol blood results from the dates August 2021- August 2022 were analysed. Only data from patients who were using TDE were kept in the study leaving 328 patients. Further information was collected from each patient's clinic notes and letters including the type and dose of hormone replacement they were taking (both TDE and the type of endometrial protection being used), whether they had AUB or not and if so, the findings of their ultrasound imaging +/- biopsy results, their Menopause Symptom Questionnaire (MSQ) score at the time of blood collection and whether or not they were using testosterone. In total, 53 data points were recorded for each patient.

To standardise the results, all forms of TDE were converted to an equivalent dose of Oestrogel pumps based on the Table 1. TDE dose and serum oestradiol levels were then compared by plotting a line graph & looking for the slope of the trendline, the correlation coefficient & at the coefficient of determination/R^2. All patients were advised not to apply oestrogen gel or spray the morning of a blood test and if using patches, to have bloods taken at least 24h after a change of patch.

To look at how bleed risk is affected by HRT, patients were divided into groups who had AUB (*n*=73) and those who did not (*n*=255). The mean TDE dose & serum oestradiol level was calculated for both groups as well as the standard deviation. The two groups were further divided by the type of endometrial protection from Mirena, Utrogestan (all doses and regimes), Hysterectomy or Other (including off license use of combination progesterone/progestogens such as Cyclogest alone (*n*=11) or in combination with oral Utrogestan (*n*=1), Mirena & Utrogestan (*n*=3) or Noresthisterone (*n*=3)). Graph1 and Table2.

A further look into the risk of AUB was investigated by dividing the patients who had a uterus in situ into two groups: those on lower dose of TDE vs high dose estrogen (HDE). Table 4. Data was also divided into lower dose and higher dose estrogen and how many were on a corresponding higher dose of endometrial protection and whether those patients experienced AUB or not (Table 3).

Finally, of those patients with AUB requiring further investigations (*n=21*), those whose investigations were complete were included for a review of their notes. Of the remaining 17 patients, 9 were on low dose TDE and 8 were on high dose of TDE. Given there were such small numbers, the findings of investigations for each patient have been detailed in Table 7.

MSQ scores were gathered for patients as close to the time just before the blood test in case dose or preparation changes were made following the blood results. Any scores further than 1 month before blood tests were discarded.

Results

There was a very weak positive correlation between TDE dose and serum oestradiol level (correlation coefficient 0.36). There was no statistical difference in either the mean TDE dose used or the serum oestradiol level in patients who had AUB or those who did not have AUB.

There was no statistical difference between mean serum oestradiol level or TDE dose in those who did or did not have AUB suggesting the likelihood of bleeding is not predictable by metrics being used at present (i.e. dose used or serum oestradiol level) but is more likely very individual to each patient.

In patients with a uterus in situ, there was no statistical difference in bleed risk amongst those on a lower dose of TDE or a higher dose of TDE. Finally, in the small number of patients who had AUB requiring further investigations, the findings of the investigations were very similar for those on lower vs higher doses apart from one patient who was on a higher dose of TDE who was found to have endometrial hyperplasia.

The slope of the trendline was 0.0022 with a correlation coefficient of 0.36 therefore showing only a very weak positive correlation between the dose of TDE and the serum oestradiol levels. The coefficient of determination/R^2 was only 0.136 meaning only 13.6% of data points fit the trendline. Based on this analysis, there was no significant positive correlation with the dose of TDE and the serum oestradiol level.

There was no statistical difference between mean pump equivalent dose (PED) of TDE for groups who did or did not have AUB. This is due to the large range in doses used which provided a range of 2.2-7.4 PED for patients with AUB & 1.8-8.0 PED for those with no bleeding using just one standard deviation (SD). Due to the large SD, it was not necessary to use a range of 2SE. Furthermore, and more interestingly, there is no statistically significant difference in serum oestradiol level between patients with or without AUB due to huge variation in serum oestradiol level. The mean dose of TDE was actually slightly lower (4.84 PED) in the women who had AUB than the women who did not have AUB (4.93 PED) despite the serum oestradiol level being slightly higher (585 in AUB patients vs 506 in patients without AUB).

After a hysterectomy, the most effective form of endometrial protection to prevent AUB was a Mirena coil (84% experienced no bleeding) followed by Utrogestan (73% experienced no bleeding).

Of patients with a uterus in situ, there was no statistical difference in bleed risk between patients on lower dose TDE or higher dose of TDE. In the group using a licensed dose of TDE, 6 out of the 9 (67%) patients had a thickened endometrium; all of which had normal histology from biopsy. Five out of eight (63%) patients in the group using higher dose of TDE had a thickened endometrium; one of which had endometrial hyperplasia. She also had fibroids and polyps and is awaiting a hysterectomy. Table 7.

The MSQ score and serum oestradiol level showed a correlation coefficient of -0.037 (non-significant). The R^2 was 0.0013 meaning that only 0.13% of results were on the trendline.

Discussion

The lack of significant positive correlation in mean TDE and serum oestradiol level amongst patients suggests both that a) women absorb TDE very differently and b) that the level of absorption and therefore serum oestradiol level is unpredictable based on the dose of TDE alone. For example, one menopausal patient's serum oestradiol on 3 PED was 1800pmol/L whereas another menopausal patient on 12 PED had a serum oestradiol of only 400pmol/L. Despite patients being given clear instructions, there are times when an anomalous result is reported and upon questioning patients have not adhered to instructions. This is negated as much as possible with clear instructions. Arguably, the varying absorption and subsequent serum oestradiol levels demonstrate that the tailoring HRT would be best based on a patient's symptoms rather than doses being limited to an arbitrary recommended cut-off point of 4 pumps of gel/100mcg patches.

It is important to remember that many factors affect absorption of transdermal medications, and this has been studied greatly. More hydrated skin better absorbs medication (Singh and Morris 2011) hence most patches form an occlusive layer creating a moist patch of skin. However, since many women complain of wrinkling and peeling of patches, they could have experienced reduced absorption. Ethnicity is known to affect absorption with Hispanic people absorbing the highest levels, followed by Caucasian people, then Asian people & finally Afro-Caribbean people absorbing the least (Leopold and Maibach, 1996). Skin metabolism too varies greatly from person to person due to various enzymes present which can affect drug bioavailability (Wester and Maibach 1989)

Furthermore, good levels of magnesium are linked with oestradiol levels. It is well known that low magnesium levels are more common in those with low oestradiol levels but the causation between them is less well established. There is evidence that the many people in the UK are chronically deficient in magnesium (Ismail, Ismail and Ismail, 2018).

It is interesting to note that standard deviation in serum oestradiol level was larger in those who did not have AUB than the range seen in the patients who did experience AUB. Fascinatingly, the range in both serum oestradiol level and TDE was so large that only one SD could be used before entering negative numbers at the lower limit. Obviously, individual patient's normal oestrogen levels throughout their reproductive years is unobtainable but the huge variation in these levels after menopause as well as a lack of correlation in either level with MSQ score further reiterates the importance of holistic management of each patient and their symptoms rather than simply following rigid guidelines.

It also suggests that after the 3-6 month settling in period following initiation of HRT or change of dose/preparation, some women simply will bleed on HRT and some will not irrespective of the TDE dose. Perhaps some women are simply more sensitive to serum oestradiol levels. Given that

oestradiol levels fluctuate so much within a menstrual cycle and interpersonally, it is difficult to establish the level of oestradiol a patient felt well with in their younger years which may impact the oestradiol level necessary for adequate symptom control in perimenopause and menopause.

The lack of statistical difference in TDE dose and serum oestradiol level in patients with or without AUB further evidences some women being more sensitive to AUB than other women, rather than the view that bleeding is due to high dose of TDE. None of the patients in this study had endometrial cancer.

In this retrospective study, many data points of 328 women who had had bloods taken for NH were analysed. It is important to remember that given there is no recommendation for the monitoring of serum oestradiol level of women using HRT that the patients who had these blood samples taken, had them done for reasons such as ongoing menopausal symptoms despite seemingly adequate doses of TDE or querying absorption of the TDE preparation they were using especially if. This makes using this group of patients to look at MSQ scores somewhat problematic due to the ongoing nature of their symptoms skewing the findings. We also did not have blood results or MSQ scores available following any adjustments made to their HRT regime to enable us to look for a difference between the two scores. Also, MSQ scores are generally completed in the days before a consultation. Some women had bloods done at a different time to their consultation and so there was not always a closely corresponding MSQ to be able to monitor changes following change to treatment regime or to link to that specific oestradiol reading. Further research looking at all serum oestradiol levels in patients, not solely those struggling with symptoms vs their MSQ score would give more applicable information.

Conclusion

Women absorb TDE very differently and the level of absorption is only very roughly associated with dose of TDE alone. This suggests tailoring HRT would be best done based on a patient's symptoms rather than the arbitrary cut off doses currently recommended. Bleed risk is even more unpredictable; our results suggest some women will bleed on HRT & some will not (after the 3-6 month settling in period following initiation of HRT or change of dose/preparation) irrespective of the dose of TDE or whether given higher doses of progesterone. This justifies the importance of treating body identical hormones used for HRT as we do other body identical hormones e.g. insulin with no upper or lower limit but instead it is tailored carefully and holistically to meet a patient's individual needs.

Ultimately, this study shows that HRT regimes need to be tailored to each individual patient based on their symptoms. If someone is struggling with ongoing symptoms despite seemingly adequate TDE dose, then perhaps in those instances their serum oestradiol level may guide the clinician to try a higher dose or an alternative HRT type. Bloods alone do not reflect the dose a patient may need as a higher serum oestradiol level may be needed for these patients to achieve good symptom control. When treating menopause in patients, individuals need to be treated holistically and clinicians should be less fearful of prescribing higher doses of TDE in cases where symptom resolution is not achieved using the current maximum licensed doses. It would be beneficial to clinicians and patients for these maximum licensed doses to be removed to enable fear-free prescribing for clinicians and alleviate some of the trepidation experienced by women who do go on to require a higher dose of TDE.

References

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Figures

Table 1: Dose equivalents of various TDE

Oestrogel (pumps)	1	2	3	4
Patch (mcg)	25	50	75	100
Sandrena (mg)	0.5	1	1.5	2
Lenzetto (sprays)	1	2	3	4

Graph 1: Type of Endometrial protection & presence of AUB

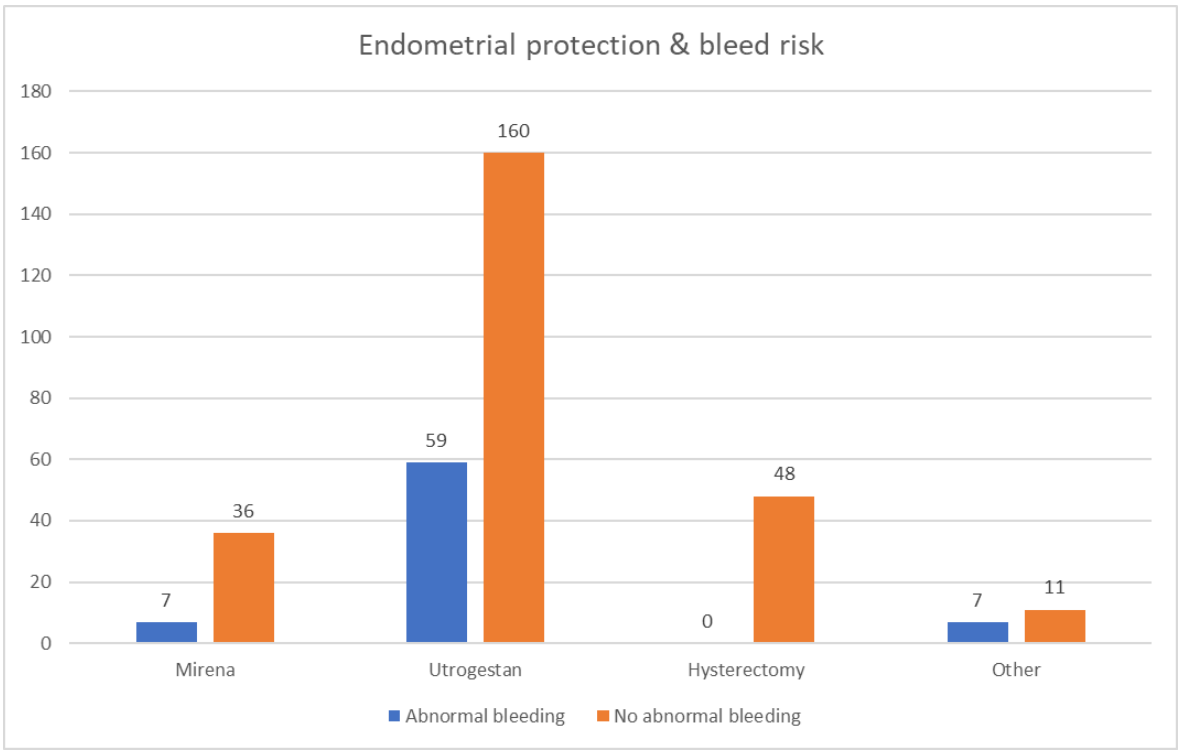


Table 2: Type of Endometrial protection & risk of AUB

Endometrial protection	AUB- % (total number)	No AUB- % (total number)
Mirena	16% (7)	84 % (36)
Utrogestan	27% (59)	73% (160)
Hysterectomy	0% (0)	100% (48)
Other	39% (7)	61% (11)

Table 3: Licensed doses of TDE & corresponding endometrial protection.

	Total number of patients	Total on licensed dose endometrial protection	Total on HIGHER dose endometrial protection
Licensed dose of TDE & No AVB	127	122	5
Licensed dose of TDE & AVB	40	33	7
Higher than licensed dose of TDE & No AVB	80	75	5
Higher than licensed dose of TDE & AVB	33	27	6

Total women on licensed TDE dose	167	Of which have AUB	24%
		Of which have No AUB	76%
Total women on HIGHER than licensed TDE dose	113	Of which have AUB	29%
		Of which have No AUB	71%

Table 4: Dose of TDE & AUB risk excluding patients who had had a hysterectomy.

	Mean oestradiol level	Mean TDE
On higher than licensed dose TDE	710	7.6
On licensed dose TDE	388	2.9

Table 5: Mean oestradiol level for those on licensed & above licensed dose of TDE

	Abnormal bleeding	No abnormal bleeding
Average Oestradiol level	585	506
Standard deviation	513	495
Range (1SD)	72-1098	12-1000
Average TDE dose	4.84	4.93
Standard deviation	2.6	3.2
Range (1SD)	2.2-7.4	1.8-8.0

Table 6: Mean dose TDE & mean serum oestradiol level & bleed risk

Table 7: Findings for patients who had investigations for AUB

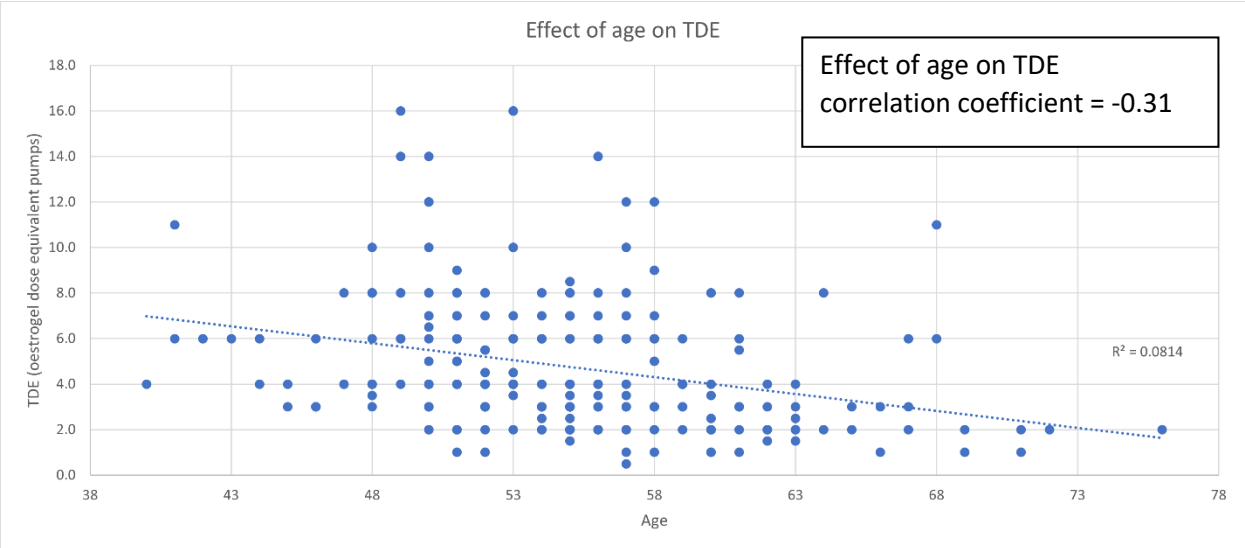
Patients on licensed dose TDE

1. Thickened endometrium 10mm- biopsy normal.
2. Fibroids, adenomyosis, thickened endometrium 8mm- biopsy normal.
3. Adenomyosis only.
4. Fibroids, thickened endometrium 7mm- biopsy normal.
5. Fibroids, thickened endometrium- biopsy normal.
6. Thickened endometrium- biopsy normal.
7. Polyp only.
8. Thickened endometrium- biopsy normal.
9. Polyp only.

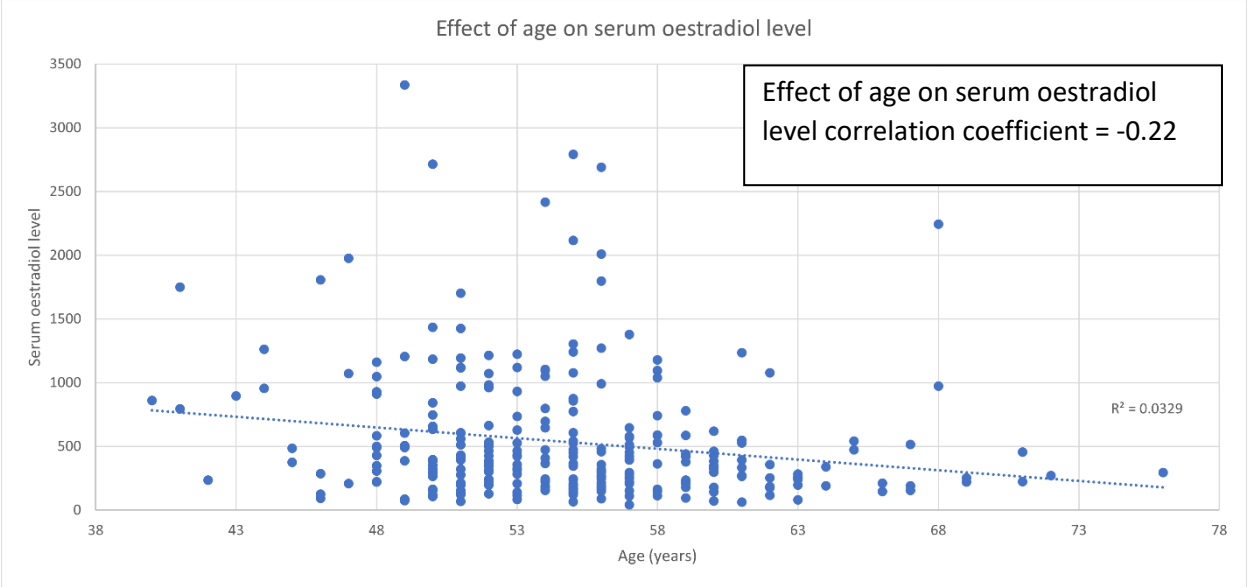
Patients on HTLD of TDE

1. Fibroids, polyps and thickened endometrium 10mm- biopsy showing endometrial hyperplasia. Hysterectomy planned.
2. Fibroids, polyps.
3. Thickened endometrium- biopsy normal.
4. Thickened endometrium- biopsy
5. Fibroid, thickened endometrium- biopsy normal.
6. Thickened endometrium- biopsy normal.
7. Adenomyosis only.
8. Fibroids, endometrium <4mm.

Graph 2: Effect of Age on TDE dose

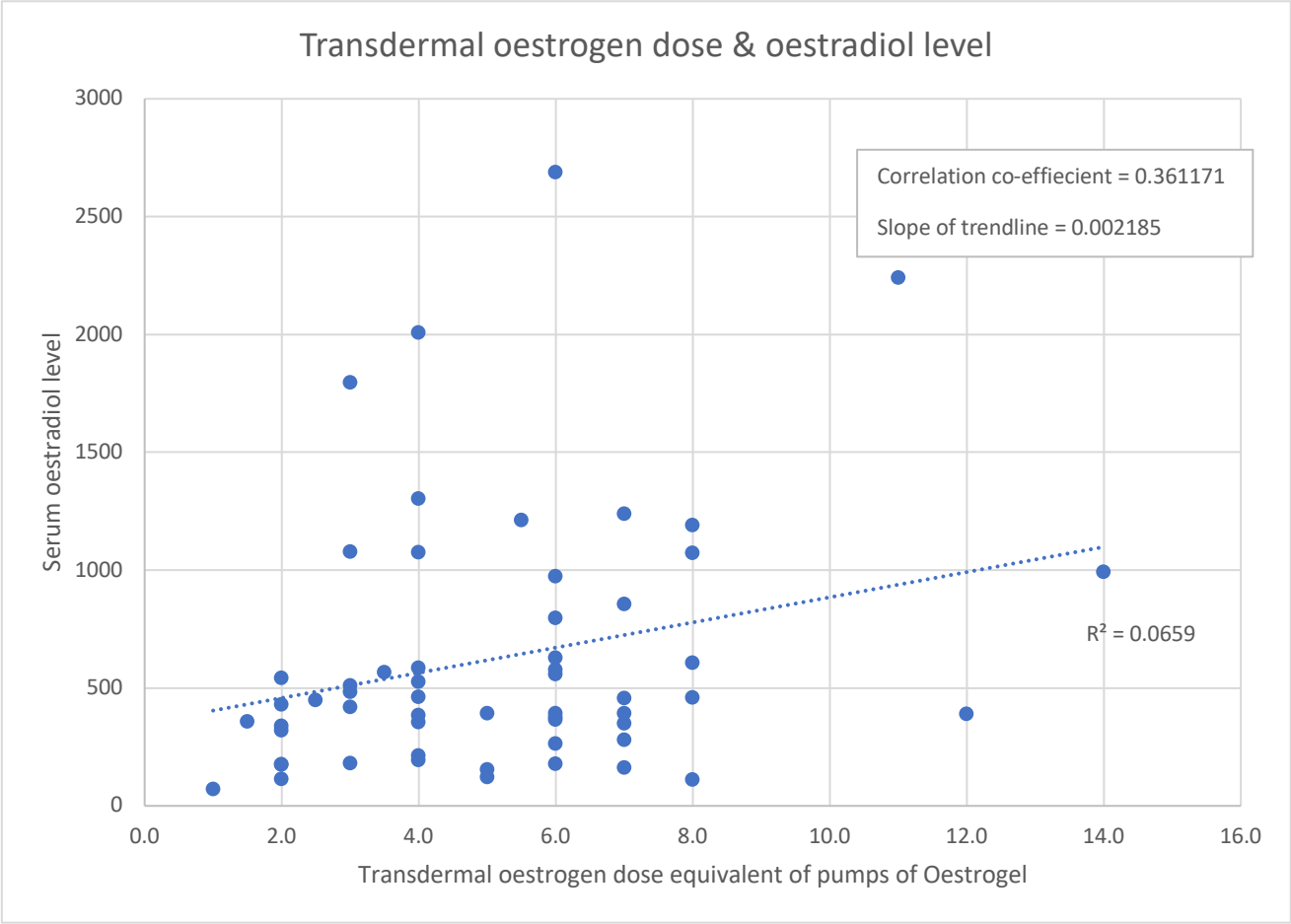


Graph 3: Effect of age on serum oestradiol



Graph 4: TDE dose & serum oestradiol level

- correlation coefficient transdermal E & oestradiol level = 0.36
- slope of trendline for transdermal E dose & oestradiol level = 0.0022



Graph 5: Serum oestradiol level & MSQ score

- correlation coefficient = -0.037
- R^2 = 0.0013