Author’s response to reviews

Title: A succesful pregnancy following SEM fine tuning of hormonal priming

Authors:

Susan SM Adams (susan@anatomy.usyd.edu.au)
Christopher CR Murphy (histology@anatomy.usyd.edu.au)

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PDF covering letter
A successful pregnancy following SEM fine tuning of hormonal priming

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Authors:
Susan SM Adams (susan@anatomy.usyd.edu.au)
Christopher CR Murphy (histology@anatomy.usyd.edu.au)

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Prof Ian Cooke Reviewer:

A paper of considerable general medical or scientific interest
Level of interest:
Other (see below)

Advice on publication: The paper uses scanning electron microscopy to
monitor changes in endometrial features that are the most sensitive indicators of potential for
implantation. It is a case report of implantation after modification of the best indicator in the
light of earlier treatment in a particular patient.

1. Page 0, para 1, l.2 P is used as an abbreviation for progesterone but is used throughout to
signify progestogen. The distinction should be made.
The abbreviation ‘P₄’ has now replaced all references to progestogen.

2. 2, l. 1" woman". We are not told whether the woman was ovulatory and suppressed or
anovulatory.
The woman was ovulatory and not suppressed and this explanation has now been added to
Materials and Methods’, Page 3, para 1.

3. l.3 "several" We are not told whether the embryos were from her oocytes or donated
oocytes or how many of each in what sequence.
“several” translates to 3 previous failed attempts at ET with 2-3 embryos in each attempt,
followed by failure of implantation.
We have now specified that they were her own embryos in ‘Materials and Methods’ Page
3, para 1. However, since this is a morphological paper and not an IVF methodological
paper we have elected not to focus on embryo transfer techniques.

4. Clarify the paragraph. The words used were several, consecutive, 3 consecutive cycles
and the fourth consecutive cycle. What was the regime in the fourth cycle, was it a
repeated third cycle? This is important.
The word ‘several’ has now been clarified in (3).
We believe the words consecutive, 3 consecutive cycles and a fourth consecutive cycle are
used correctly in Page 1, para 2 ‘Results’.
The regime in the fourth cycle has now been better clarified in Page 8, para 2,
‘Conclusion’.

5. To draw appropriate inferences it needs to be stated whether the eggs or embryos were
donated and whether conception took place in the first or second cycle at the optimum
dose of the regime.
The embryos were her own (refer to point (3).
The text refers to ‘cryopreserved embryos from previously failed attempts at ET prior to
the commencement of treatment’. We do not believe it benefits the paper to further state
that ET was not attempted during the 3 treatment cycles. Implantation however, did occur
during the fourth consecutive treatment cycle – (refer point 4).

6. Did the pregnancy proceed to viability?
Both the Results Page 1, and the Conclusion Page 8 have stated that the woman ‘gave birth to a healthy child’. The title of the paper “successful pregnancy…..” also reflects the outcome.

7. The conclusion is inappropriate. A success "rate" requires more than one case. Depending on whether conception occurred on the first or second optimum treatment cycle other explanations need to be considered for a possible failure in the first optimum treatment cycle and that would weaken the claim. The use of the word ‘rate’ – Page 1, para 3 Conclusion, has now been changed to read “successful outcome”. Implantation occurred in the 4th treatment cycle. Embryo transfer was not attempted during the 3 treatment cycles – refer points 4 and 5.

8. Monitoring is appropriate (in spite of the rapid turnaround in expensive resources- the practicability and cost of this are not discussed). Monitoring is appropriate, which is the basis for this paper. However, cost and practicability would vary greatly both between IVF Centres and countries.

9. "clearly demonstrates" needs "in this case" placed after it. The technique "could", not "should" be used...
   “in this case” has been added as suggested – Page 1 Conclusion. The word ‘could’ has now replaced the word ‘should’ – Page 1, Conclusion

10. Page 1 para 1 Does repeat biopsy in consecutive cycles have an impact on pinopode formation?
    The entire uterine epithelium is sloughed off and regenerated every 28 days or so, and as such, the newly regenerated epithelium under hormonal influence, reproduces its morphological appearance precisely. Neither repeat biopsy nor currettage have been shown to affect this process.

11. "uterodomes" could usefully have "pinopodes" placed after it. Presumably the authors are trying to change the nomenclature. If so they should be consistent in their spelling of uterodomes which is variably spelt throughout.
    The spelling of ‘uterodomes’ has been corrected and the word ‘(pinopod) ‘has been added as suggested.

12. Page 2, para 2 1.2 ? an important consideration
    This comment refers to the recognition of tissue inhomogeneity in the text and does not require further comment. Page 3, para 2

13. l.3&4 expand "uterodome analysis"
    Introduction, Page 3, para 5 has now been rewritten and ‘uterodome analysis’ removed.

14. Page 3 para 3 1.4&5 and para 3 1.1&2 PO4 is better
    PO4 has been removed altogether and replaced with ‘phosphate buffer (PB)’.

15. Page 4 para 1 1.1&4” inhomogeneous”
    This word has now been correctly spelled as suggested, Page 5, para 1 Results.

16. Page 5 para 1 1.1 and 7 How do "deep crevicing " and "cell separation was not apparent" match? Please explain.
    These terms refer to morphological terminology when observing epithelial tissue. ‘Deep crevicing’ refers to large areas of tissue whereas ‘cell separation’ refers to singular cells.
17. 2.1.6 post-ovulatory
   Page 6, para 1, Discussion. The word ‘post ovulatory’ now reads ‘post-ovulatory’.

18. Page 6 para 11.1 Please expand on "previously impoverished". Because the pt. was
    anovulatory, or non-responsive to particular doses? It would be useful to speculate as to
    why.
    Page 6, para 2, line 13. Speculation was not expanded on in the text, however, it is
    probable that the woman was unstimulated because her own hormones were insufficient to
    provide threshold levels from the ovaries, as in perimenopause, perhaps due to her age.

19. 2.1.8 If the third and ?fourth cycles were at the same dose, was there variation in response?
    i.e. individual variation in response?
    It is not possible to determine if there was variability between the 3rd and 4th cycles
    because the 4th cycle was an embryo transfer cycle and as such could not have a biopsy.
    The literature supports the theory that after several consecutive hormone supplementation
    cycles, the variability between cycles is reduced.

20. Page 7 para 2 How much could the poor response have been due to the Provera and how
    applicable are these data likely to be to the use of Progesterone?
    It was not within the scope of this paper to compare the differing effects that progesterone
    may have produced in comparison to Provera. The doses of Provera that were used
    initially, are standard doses given to IVF patients in preparation for ET. AND this is the
    point of the paper, that standard doses – because of individual patient response, do not
    always produce the desired effect on the uterine epithelium and therefore tailoring the
    dose is suggested.

21. 1.11 "four fold" Is this a simple log biological response?
    The word has now been more correctly spelled – fourfold. It is an English term meaning
    ‘multiplied by four’, Page 8, para 1

22. Conclusion
    1.5 three consecutive
    1.7&8 4th consecutive again
    1. 9 "case by case" is more precise.
    Page 8, Conlusion. These points have previously been addressed - refer to point 4.

23. The authors could make a plea that this approach could be used more widely. Those data
    may then address the within- and between-patient variation, which has been such a
    problem in this field, at least with respect to light microscopy, as also shown here.
    We have made reference to a previous paper -Adams, S.M., et al (2001) Manipulation of
    the follicular phase: Uterodomes and pregnancy - is there a correlation? BMC
    Pregnancy and Childbirth 1:2 (17 Jul).

24. The Table and Figure are necessary and should remain unchanged.

25. The spacing of the references is erratic.
    The Reference spacing has been adjusted

Competing interests:
None declared.