Executive Summary

1. Purpose

Human placental extracts (HPE) have been widely used in various diseases for a long time but criticized for the lack of clear evidence for clinical effectiveness and safety, which has caused controversies in the society. This study was performed

1) to review the results of domestic and foreign studies through the systematic reviews and, based on these results, to provide recent evidences for clinical effectiveness and safety of HPE

2) to understand the actual state of using human placenta injection (HPI) and social recognition for HPI through the survey, and then to provide accurate information to medical staffs, patients, and interested parties all related to the use of HPI.

2. Methods

1) Systematic review

For assessing literatures related to clinical effectiveness and safety of HPE.

- The following 26 domestic and foreign electronic database (DB) were searched (1950-2009) and additional hand search was performed.

Domestic (19 DB)	Foreign (7 DB)
KoreaMed	Ovid-Medline
KMbase	EMBASE
OASIS	The Cochrane Library
KTKP	CINAHL
National Assembly Library	CAJ (China Medical Journal; CNKI)
The National Library of Korea	ICHUSHI(医学中央雜誌)

National Digital Library Korea Knowledge Portal KERIS NDSL thesis.or.kr KISTI	Medical Online(Japanese medical literature DB)

- Administration route and study design, study period, and language were not limited.
- Inclusion/exclusion, the quality assessment and the data extraction was performed by two investigators per each language independently.
- The quality of literature was evaluated by using quality evaluation tools such as SIGN in case of study designs with different comparison (randomized controlled trials, non-randomized controlled trials, cohort study, case-control study) or MINORS in case of study designs with same or no comparing subjects(cross-sectional study, before-after study, interrupted time series, non-comparative study), and then the evidence level for each disease group was determined comprehensively.
- Data was extracted by one investigator per literature using a standardized format, and then complemented by another investigator.

2) Social recognition survey

The survey was performed for the recognition and actual use of HPI in adult females of 19~69 years in the country.

- survey period : 2009. 10. 7～12
- sample size : 1,000
- sample error : 95% confidence level, ±3.1%point
- sampling : proportional quota sampling by age and region
- survey method : telephone interview and online survey

The survey questionnaire was divided into 4 sections, which consisted

of 3～10 questions.

- general characteristics
- actual state of using HPI by experienced subjects
- recognition on HPI by non-experienced subjects
- intention of using HPI in the future

Frequency and percentage were calculated for experience of HPI, indications of experienced subjects, costs, experience of adverse effects, recognition for HPI by non-experienced subjects, and intention for use in the future. Chi-square test was used to examine the difference in proportion of the number of use by age group and future intention for use according to the experience of human placenta injection.

3. Results

1) Systematic review

A total of 144 literatures were selected by performing inclusion/exclusion after the search. Among 144 literatures, only 38 studies(26%) were randomized clinical trials (RCT) and the other 106(74%) studies were non-RCT or cross-sectional studies or non-comparative studies.

A total of 139 literatures for 28 disease groups and 1 group of another disorders that were difficult for classification were included in the quality evaluation, 5 case reports which reported adverse drug reactions only were separately arranged.

Table 1. Human placental extracts uses of 29 Disease groups

▪ miscarriage (4)	▪ other respiratory diseases (3)
▪ hypogalatia (5)	▪ immune function (2)
▪ dysmenorrhea (3)	▪ cancer (4)
▪ menopausal disorders (9)	▪ anemia (3)
▪ pelvic inflammation (2)	▪ eye disease (9)
▪ vulvar and cervical diseases (5)	▪ paralysis (4)
▪ tubal obstruction (2)	▪ sleep disorder (3)

▪ other ob&gy disease: emesis gravidarum (1)	▪ postoperative pain (2)
▪ arthritis (7)	▪ vitiligo (9)
▪ rhinitis (7)	▪ burn, ulcer, wound (13)
▪ oral disease (6)	▪ urticaria (3)
▪ periodontal disease (2)	▪ alopecia (2)
▪ liver diseases (6)	▪ other skin disorders (4)
▪ gastric ulcer (2)	▪ other disorders (19)
▪ asthma (5)	▪ safety: adverse drug reactions (5 articles)

We divided and ordered by the disease groups if an article includes various disease groups, therefore, number of included studies (N=144) are differ from sum of studies (N=151)

Burn, ulcer, and wound were the highest (13 articles) as single disease group, and the methods for applying human placenta were varied including parenteral (intravenous injection, intramuscular injection, herbal acupuncture) and non-parenteral (oral, local application) methods. As for quality assessment, there was no study which was evaluated as good quality evidence (++) with all or almost all criteria were satisfied, and most of studies (86%) were evaluated as low quality (-) with all or almost all criteria were not satisfied. When the evidence level was evaluated by examining the evidence level and effective direction, and the number of studies in the literatures selected for quality evaluation, there was no ‘randomized clinical trial with very low possibility of bias (1++)’ in all disease groups.

2) Social recognition survey

Among all adult females, 9.5% experienced HPI. For ages of its use, the 20s～30s took 50% of the users, and indications were in the order of skin beauty, recovery from fatigue, and alleviation of menopausal symptoms. Among 95 subjects who used human placenta injection, 9 subjects(9.5%) reported that they experienced adverse effects. Among non-experienced subjects, 79.3% responded that they knew HPI by people around them, media·newspaper articles, and Internet. 46.3% of experienced subjects and 32.5% of non-experienced subjects for HPI

answered for intention of using HPI in the future, and the main reason for no intention of using HPI was the uncertainty of effectiveness and safety.

4. Discussion & Conclusion

This systematic review is significant in that it systematically organized and presented currently possible evidences for HPE for the first time, and through the survey, it was possible to understand the basic information on the social recognition for the current state of the use, effectiveness, and safety of HPI in adult females in the country. On the whole, it is difficult to conclude that HPE have clinical effectiveness and safety because the amount of evidence for off-label disease was insufficient and the quality was low. Also in the survey, HPI is widely used for off-label indication, the reason for no intention of using HPI was the uncertainty of effectiveness and safety.

The results from this study will be able to provide basic data to the medical society, decision makers and consumers to help make educated decisions about the safety and efficacy of HPE. This study suggest that further official measures must be taken in order based on the results that shows HPE are being used for purposes not included in the KFDA indication. Also, the importance of advertising the risk of HPE use outside the KFDA indication is being suggested by this research. In case of two indications(menopausal disorder and liver diseases) sanctioned by KFDA, the comparative effectiveness research(CER) on HPE's effects and safety would be needed.

Also, the medical society must be able to make ethical decisions about using HPE with scientific evidences. More scientific approach must be taken in terms of HPE use to build up scientific evidences behind the safety and efficacy of HPE. Therefore, strengthened education is needed among the medical society to educate its members about the safety and efficacy of HPE prescription.

This study was able to provide scientific evidences and proposed a social solution model based on those evidences. Further randomized controlled clinical studies as well as studies on CER of HPE must be performed to provide evidences to back up its efficacy and safety. Also, management structure to compensate with scientific evidences is needed for further regulation of HPE use.